<u>FIGURE 1</u>

TGGCCTCCCCAGCTTGCCAGGCACAAGGCTGAGCGGGAGGAAGCGAGAGGCATCTA
AGCAGGCAGTGTTTTGCCTTCACCCCAAGTGACC<u>**ATG**</u>AGAGGTGCCACGCGAGTCTC
AATCATGCTCCTCCTAGTAACTGTGTCTGACTGTGCTGTGATCACAGGGGCCTGTGA
GCGGGATGTCCAGTGTGGGGCAGGCACCTGCTGTGCCATCAGCCTGTGGCTTCGAGG
GCTGCGGATGTGCACCCCGCTGGGGCGGGAAGGCGAGGAGTGCCACCCCGGCAGCC
ACAAGGTCCCCTTCTTCAGGAAACGCAAGCACCACACCTGTCCTTGCTTGCCCAACC
TGCTGTGCTCCAGGTTCCCGGACGGCAGGTACCGCTGCTCCATGGACTTGAAGAACA
TCAATTTT<u>**TAG**</u>GCGCTTGCCTGGTCTCAGGATACCCACCATCCTTTTCCTGAGCACAG
CCTGGATTTTTATTTCTGCCATGAAACCCAGCTCCCATGACTCTCCCAGTCCCTACAC
TGACTACCCTGATCTCTCTTGTCTAGTACGCACATATGCACACAGGCAGACATACCT
CCCATCATGACATGGTCCCCAGGCTGGCCTGAGGATGTCACAGCTTGAGGCTGTGGT
GTGAAAGGTGGCCAGCCTGGTTCTCTTCCCTGCTCAGGCTGCCAGAGAGGTGGTAAA
TGGCAGAAAGGACATTCCCCCTCCCCTCCCCAGGTGACCTGCTCTCTTTCCTGGGCCC
TGCCCCTCTCCCCACATGTATCCCTCGGTCTGAATTAGACATTCCTGGGCACAGGCTC
TTGGGTGCATTGCTCAGAGTCCCAGGTCCTGGCCTGACCCTCAGGCCCTTCACGTGA
GGTCTGTGAGGACCAATTTGTGGGTAGTTCATCTTCCCTCGATTGGTTAACTCCTTAG
TTTCAGACCACAGACTCAAGATTGGCTCTTCCCAGAGGGCAGCAGACAGTCACCCCA
AGGCAGGTGTAGGGAGCCCAGGGAGGCCAATCAGCCCCCTGAAGACTCTGGTCCCA
GTCAGCCTGTGGCTTGTGGCCTGTGACCTGTGACCTTCTGCCAGAATTGTCATGCCTC
TGAGGCCCCCTCTTACCACACTTTACCAGTTAACCACTGAAGCCCCCAATTCCCACA
GCTTTTCCATTAAAATGCAAATGGTGGTGGTTCAATCTAATCTGATATTGACATATTA
GAAGGCAATTAGGGTGTTTCCTTAAACAACTCCTTTCCAAGGATCAGCCCTGAGAGC
AGGTTGGTGACTTTGAGGAGGGCAGTCCTCTGTCCAGATTGGGGTGGGAGCAAGGG
ACAGGGAGCAGGGCAGGGGCTGAAAGGGGCACTGATTCAGACCAGGGAGGCAACT
ACACACCAACATGCTGGCTTTAGAATAAAAGCACCAACTGAAAAAA

FIGURE 2

MRGATRVSIMLLLVTVSDCAVITGACERDVQCGAGTCCAISLWLRGLRMCTPLGREGEE
C
HPGSHKVPFFRKRKHHTCPCLPNLLCSRFPDGRYRCSMDLKNINF

Important features:

Signal peptide:
1-19

N-myristoylation sites:
33
35
46

10022503.121501

FIGURE 3A

PRO	XXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXYYYYYYY	(Length = 12 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

5 divided by 15 = 33.3%

Printed from Web

FIGURE 3B

PRO	XXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXYYYYYYZZYZ	(Length = 15 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

5 divided by 10 = 50%

10027603.121901

FIGURE 3C

PRO-DNA	NNNNNNNNNNNNNN	(Length = 14 nucleotides)
Comparison DNA	NNNNNNLLLLLLLLLL	(Length = 16 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

6 divided by 14 = 42.9%

FIGURE 3D

PRO-DNA	NNNNNNNNNNNN	(Length = 12 nucleotides)
Comparison DNA	NNNNLLLVV	(Length = 9 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

4 divided by 12 = 33.3%

FIGURE 4

TGGCTCCCCAGCTTGCCAGGCACAAGGCTGAGCTGGAGGAAGCGAGANGCATCTAA
GCAG
GCAGTGTTTTGCCTTCACCCCAAGTGACCATGAGAGGTGCCACGCGAGTCTCAATCA
TGC
TCCTCCTAGTAACTGTGTCTGACTGTGCTGTGATCACAGGGGCCTGTGAGCGGGATG
TCC
AGTGTGGGGCAGGCACCTGCTGTGCCATCAGCCTGTGGCTTCGAGGGCTGCGGATGT
GCA
CCCCGCTGGGGCGGGAAGGCGAGGAGTGCCACCCCGGCAGCCACAAGGTCCCCTTC
TTCA
GGAAACGCAAGCACCACACCTGTCTTGTTGCCCAACCTGCTGTGCTCCAGTTCCGGA
CGG
CAGTACGCTGCTCA

FIGURE 5A

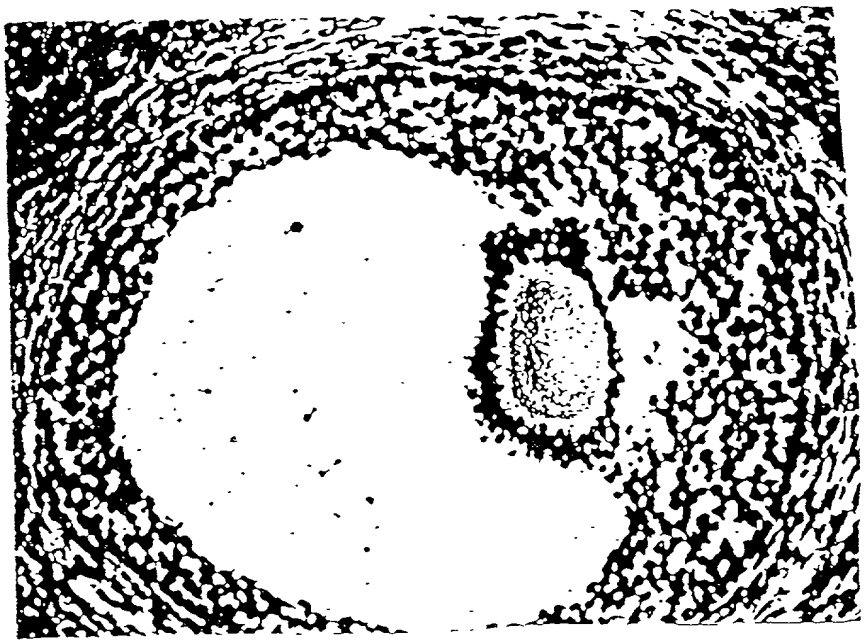


FIGURE 5B

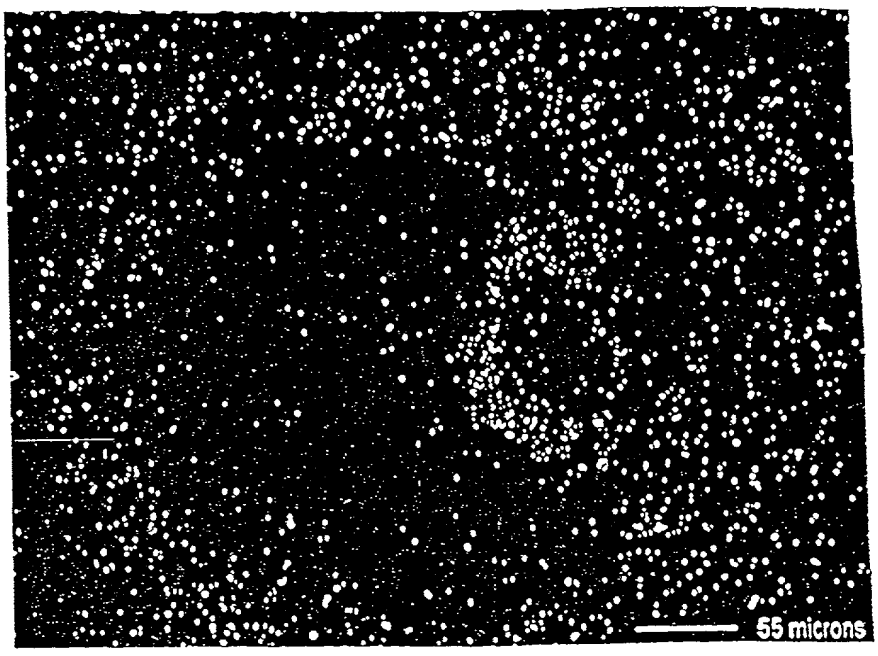


FIGURE 5C

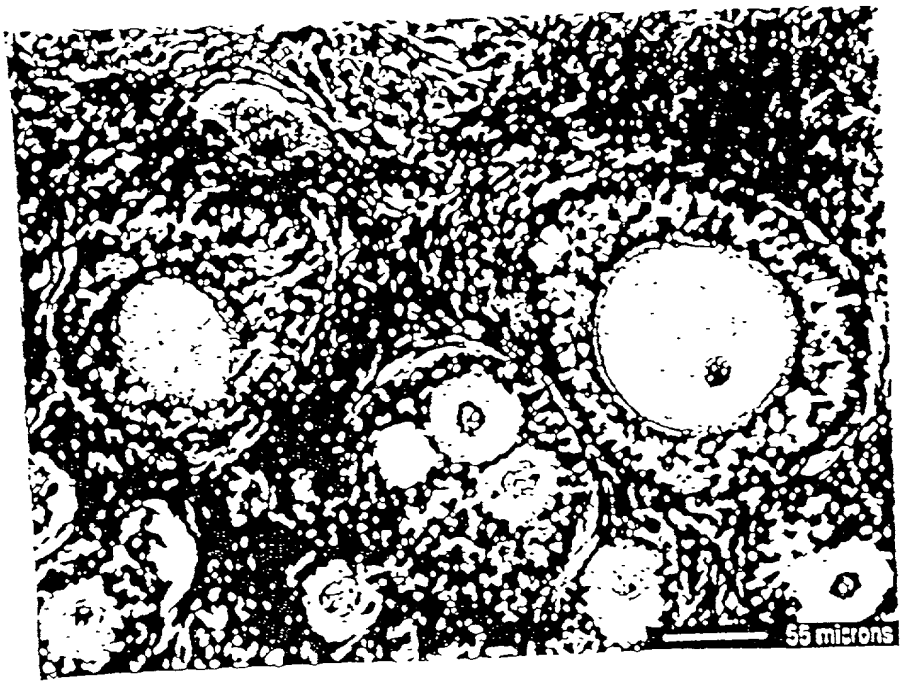


FIGURE 5D

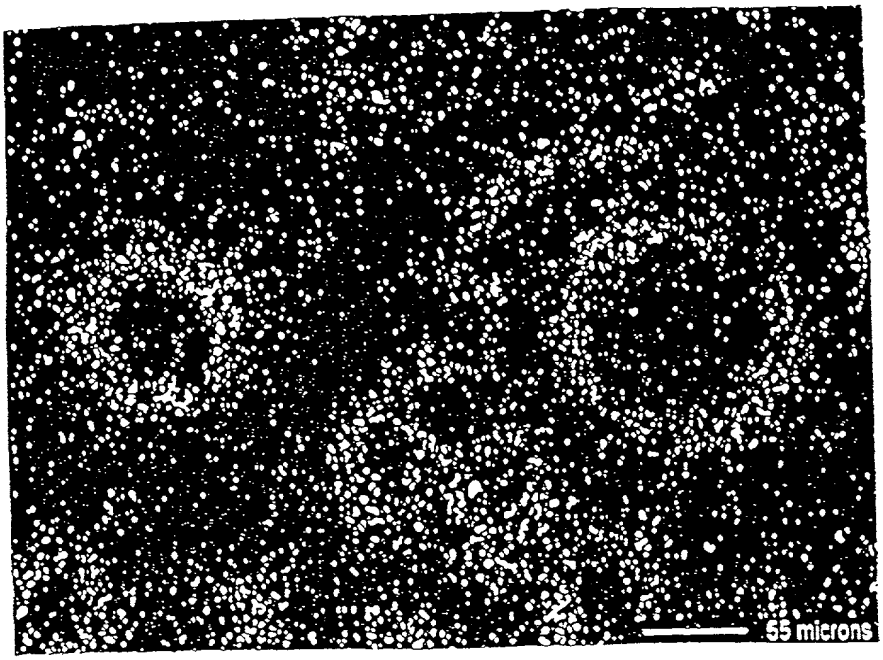


FIGURE 5E

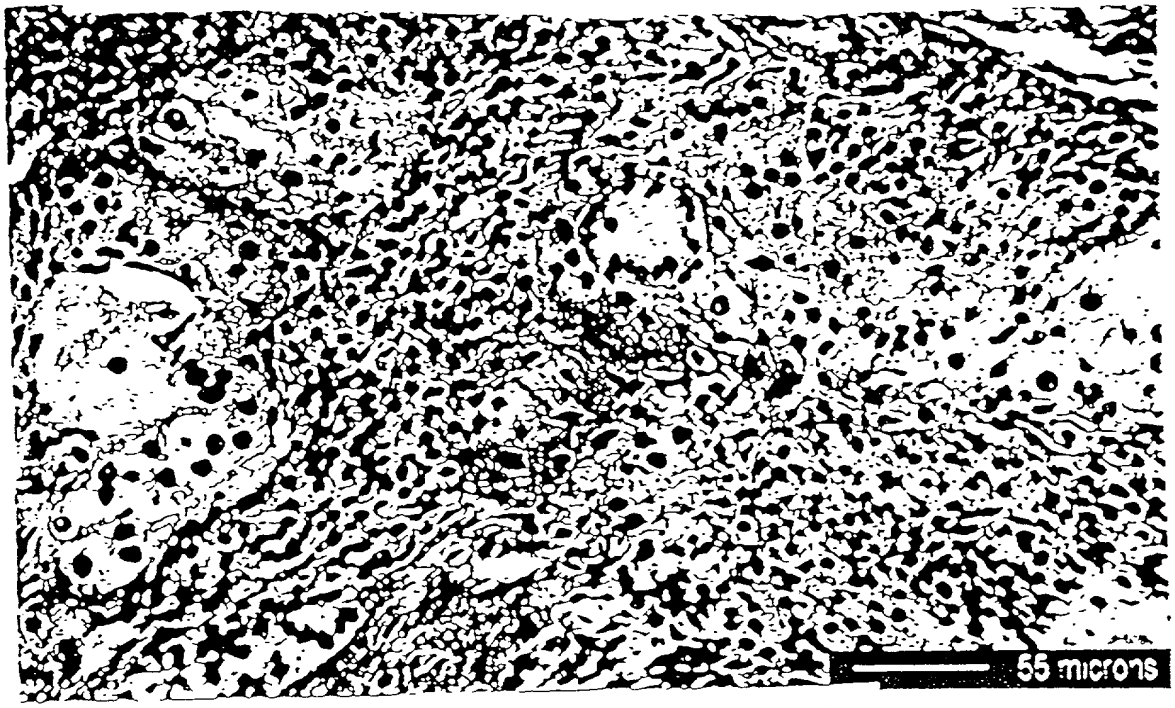


FIGURE 5F

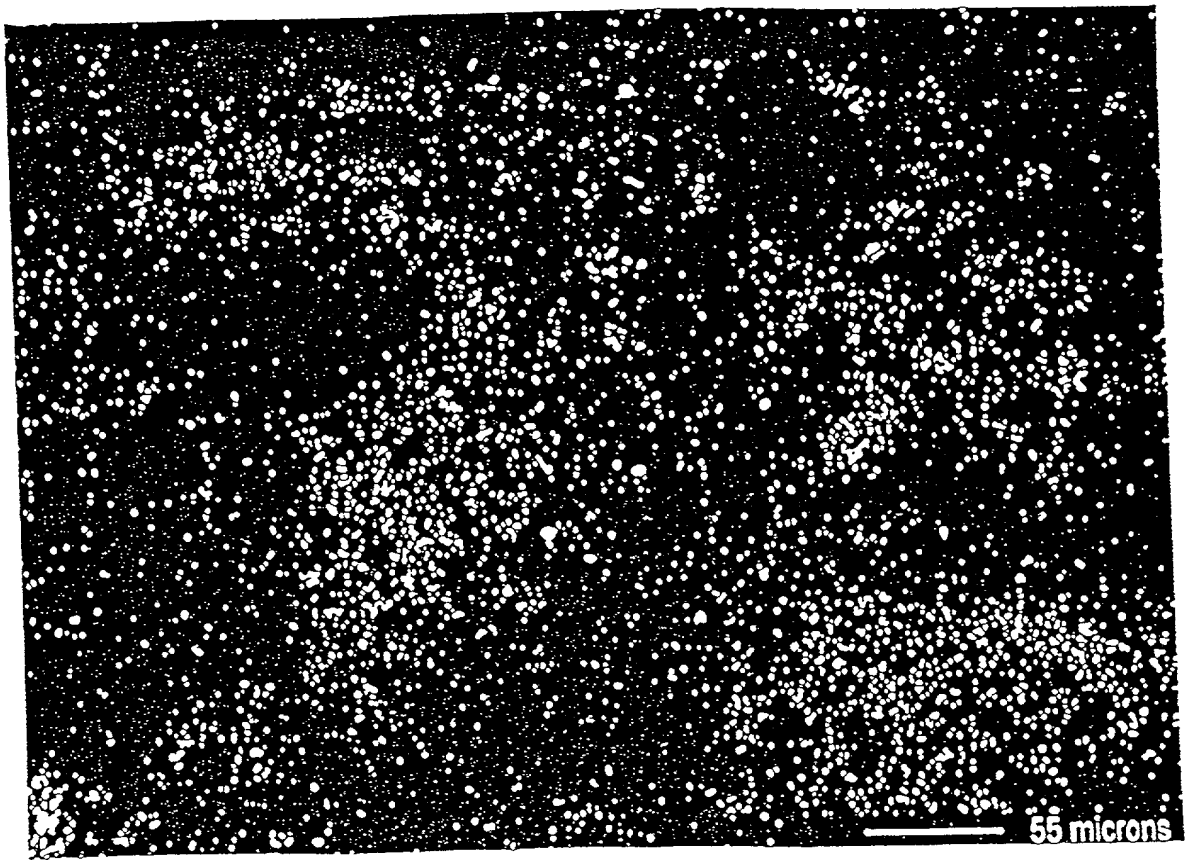


FIGURE 6A

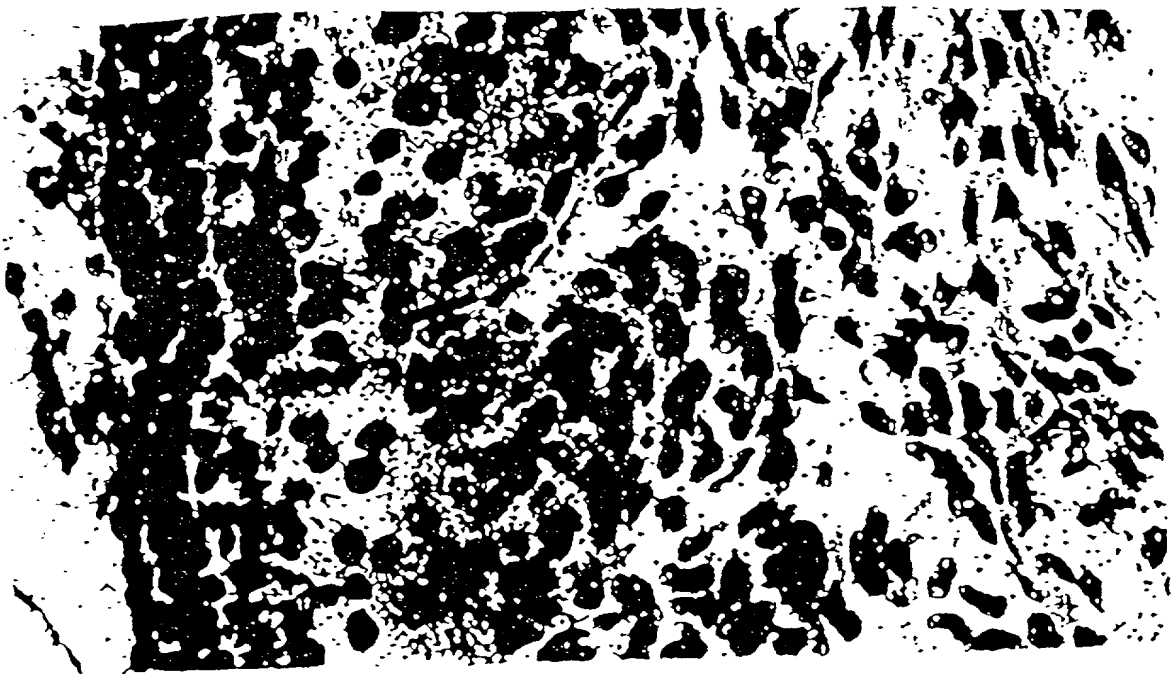


FIGURE 6B

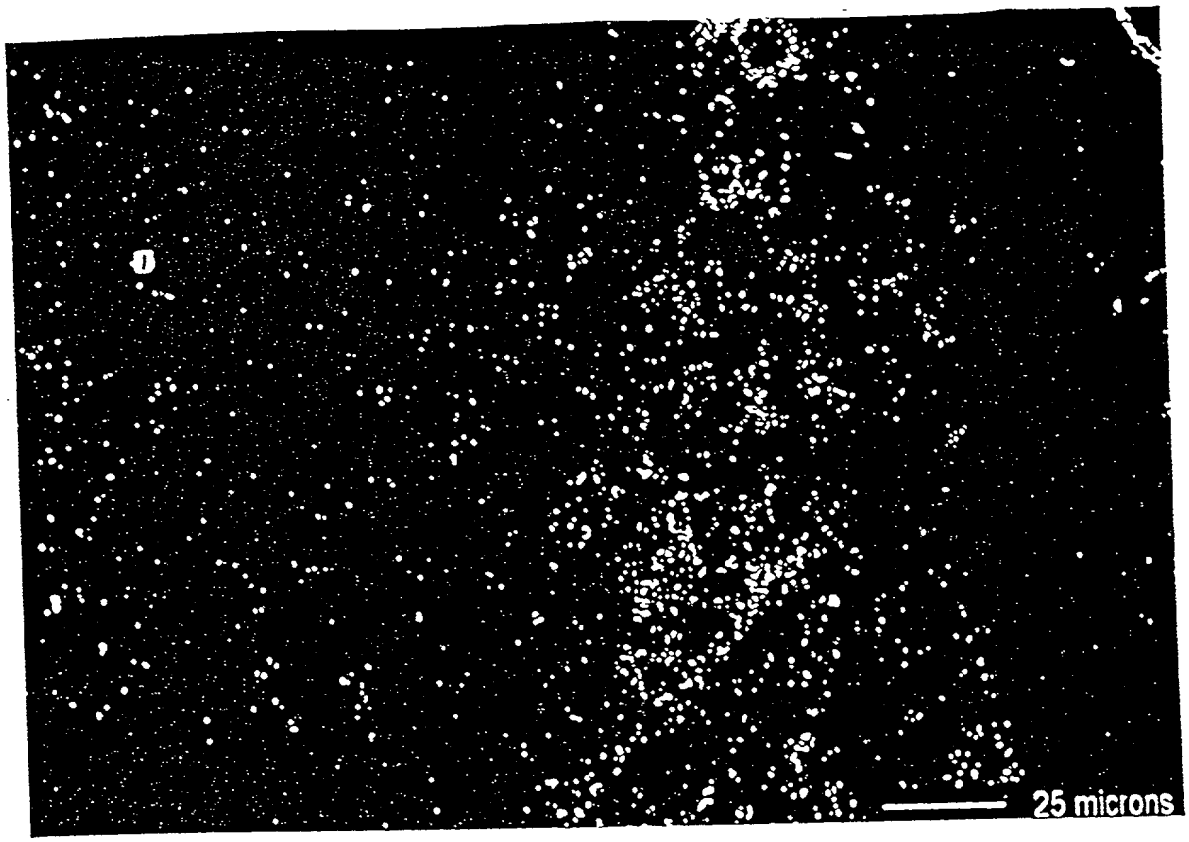


FIGURE 6C

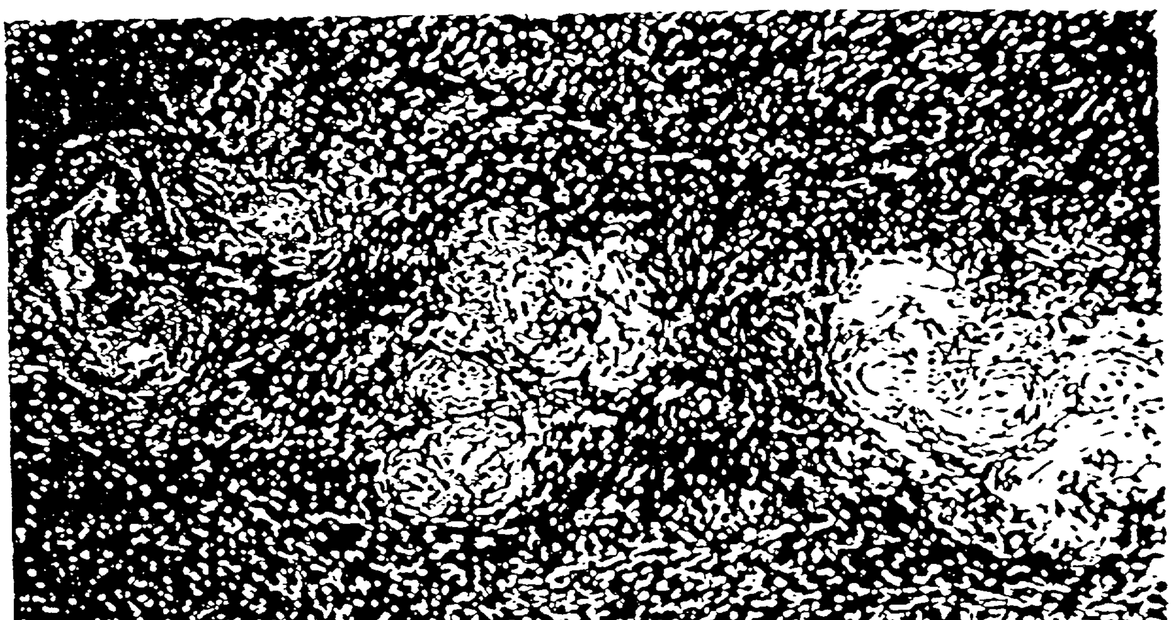
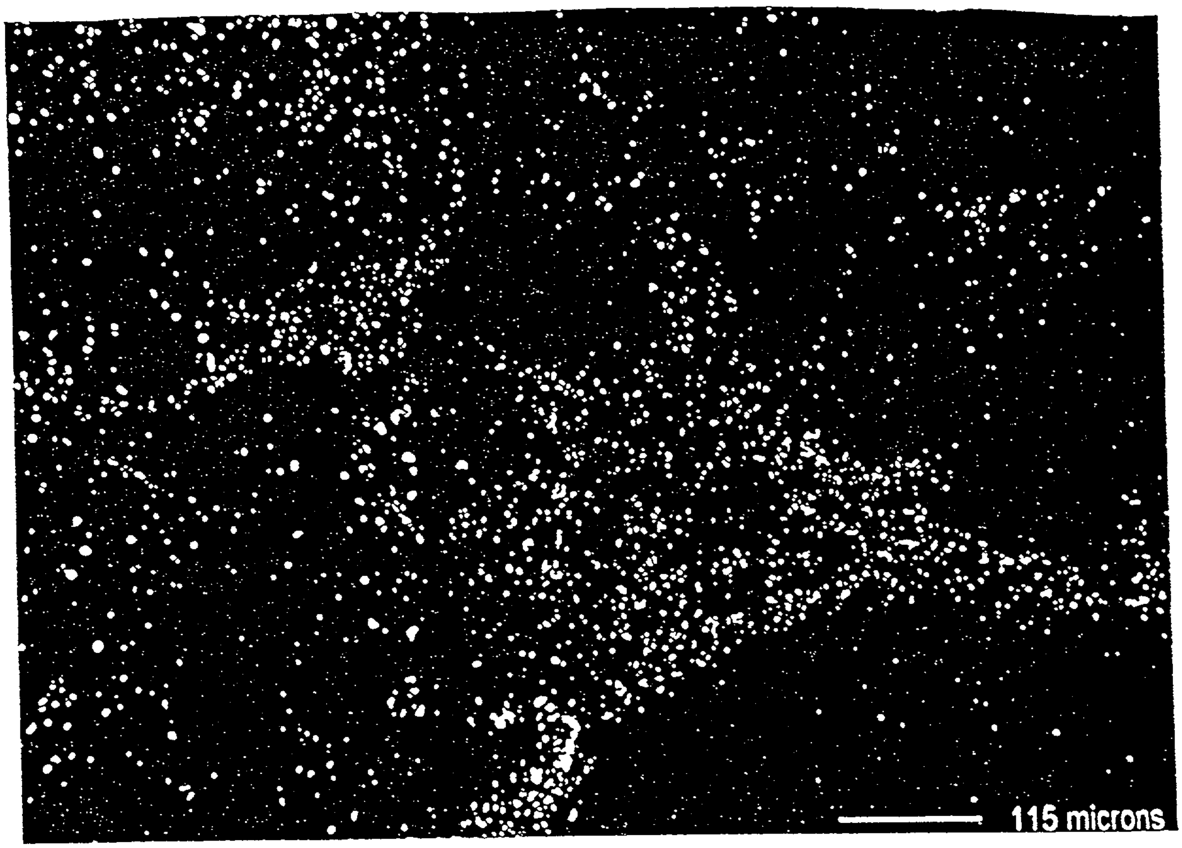


FIGURE 6D



10027603 .121501

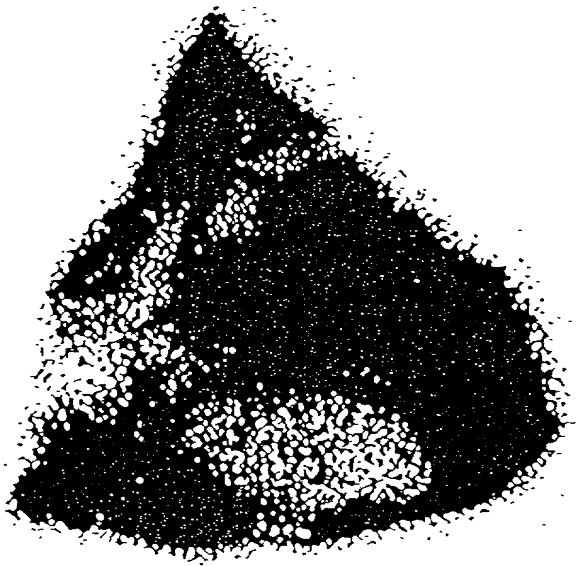


FIGURE 7A

FIGURE 7B

FIGURE 8

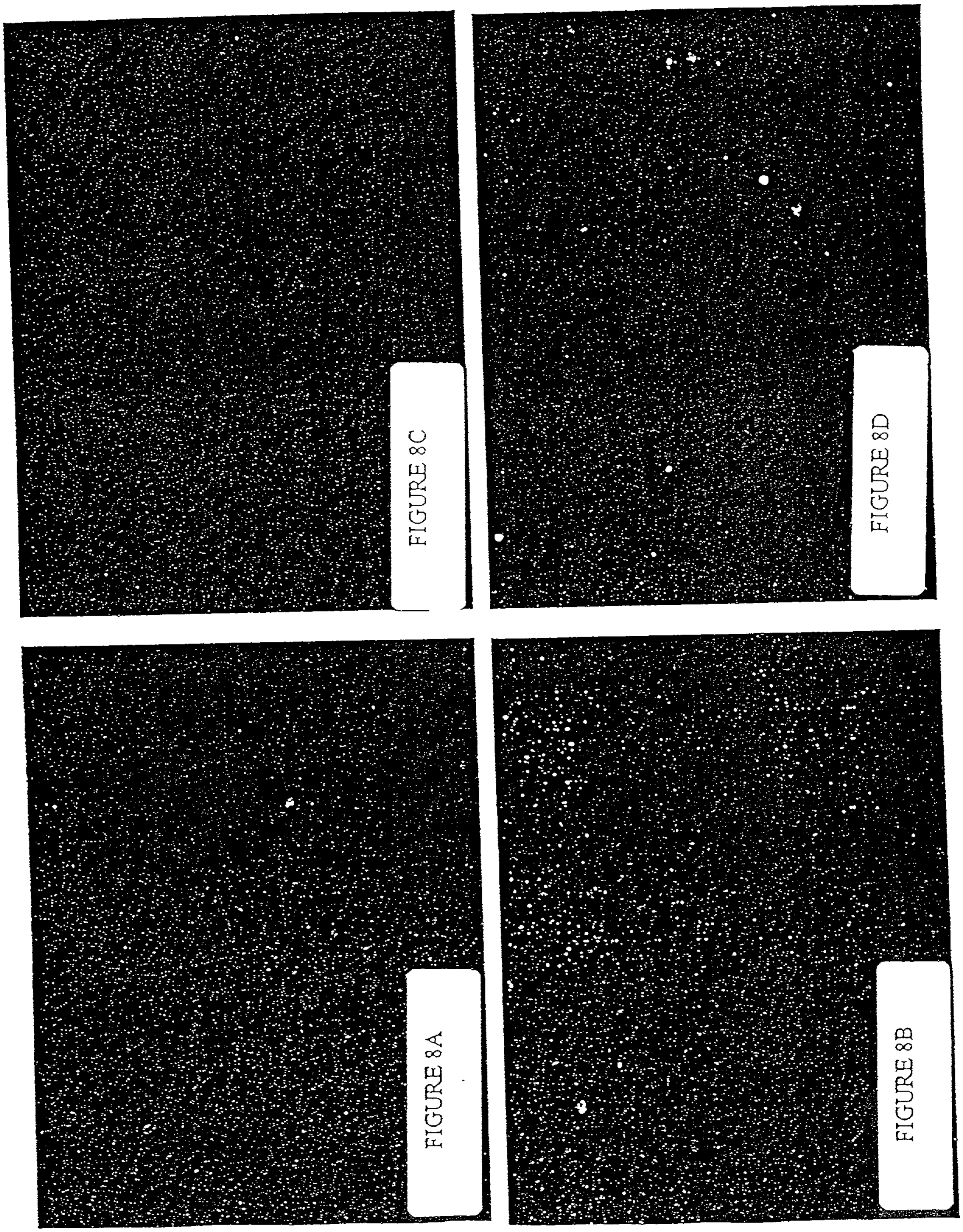
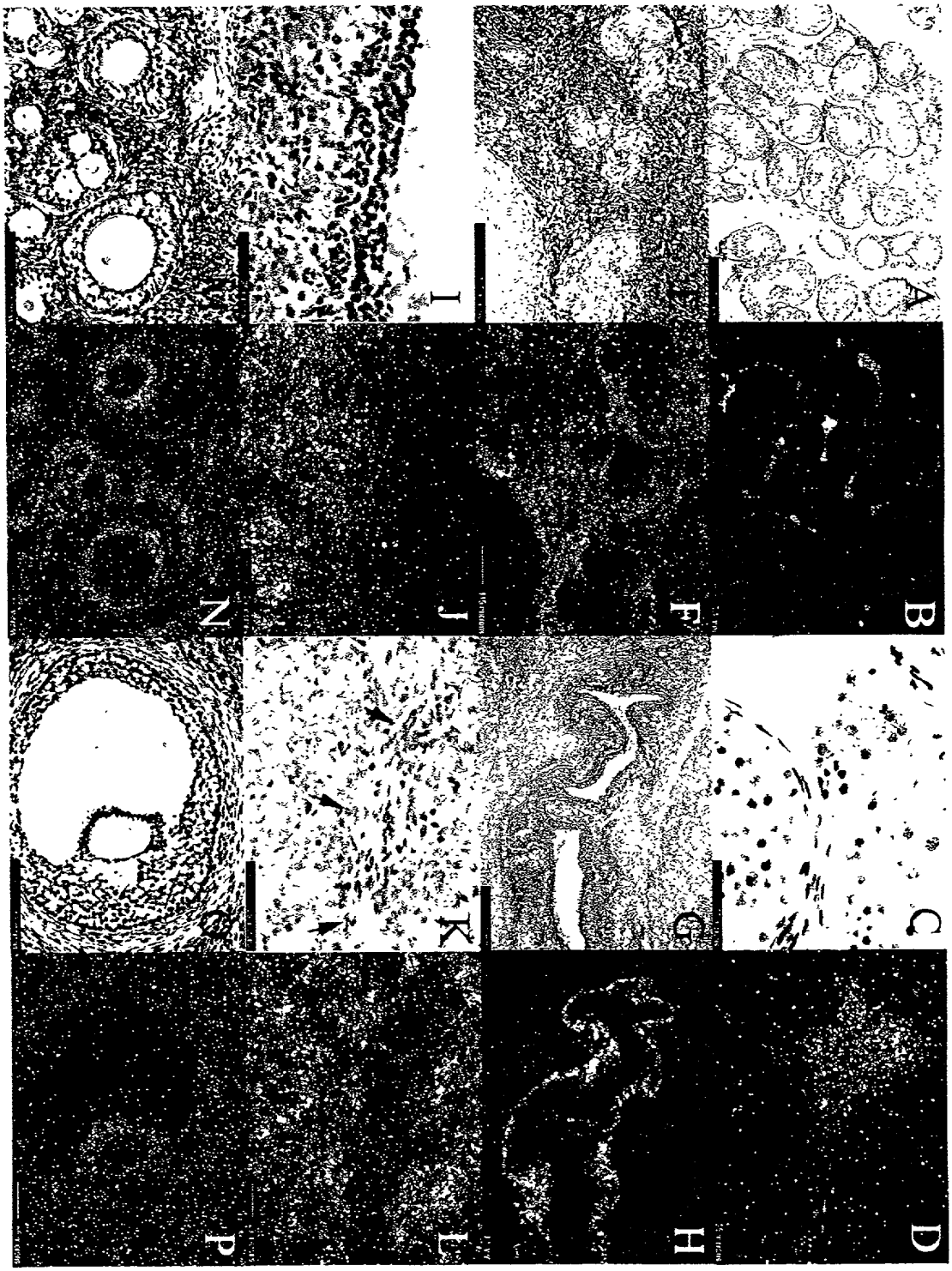
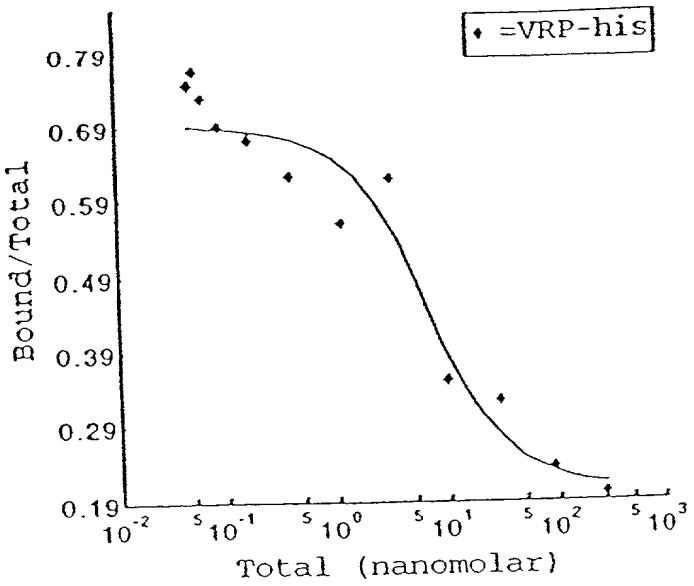


FIGURE 9



EP0376854A1

FIGURE 10 A



Kd= 1.43 +/- 0.4 nM

FIGURE 10 B

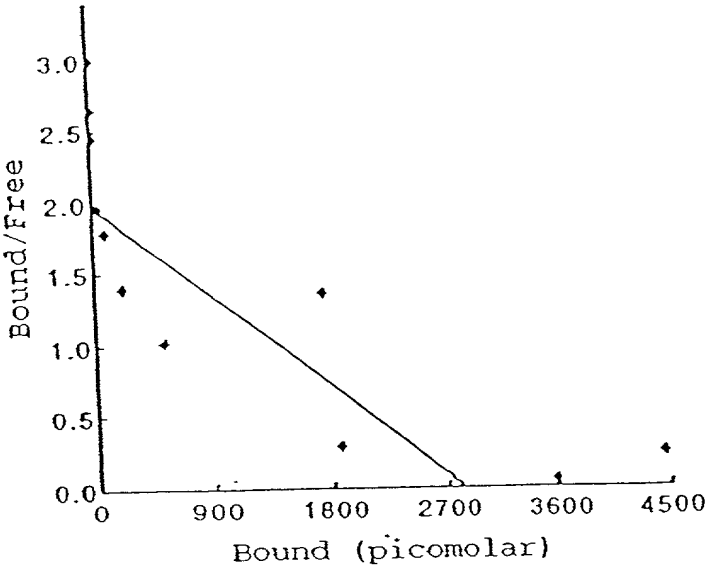
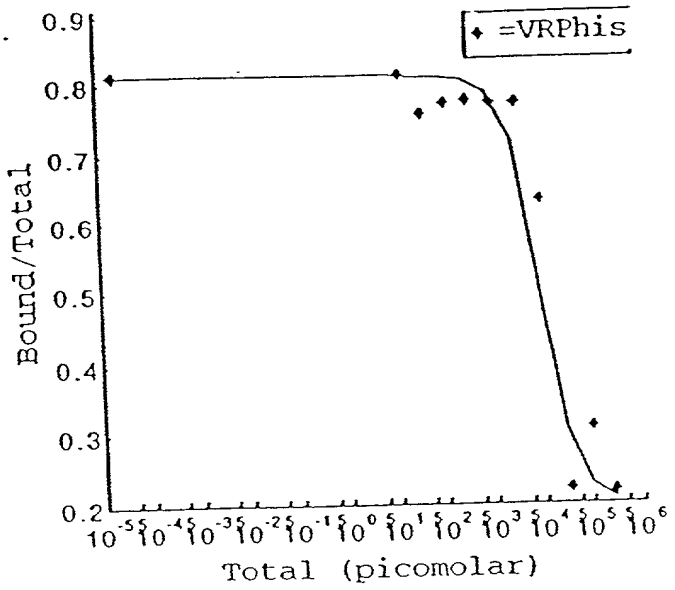


FIGURE 11 A



Kd= 0.95 +/- 0.6 nM

FIGURE 11 B

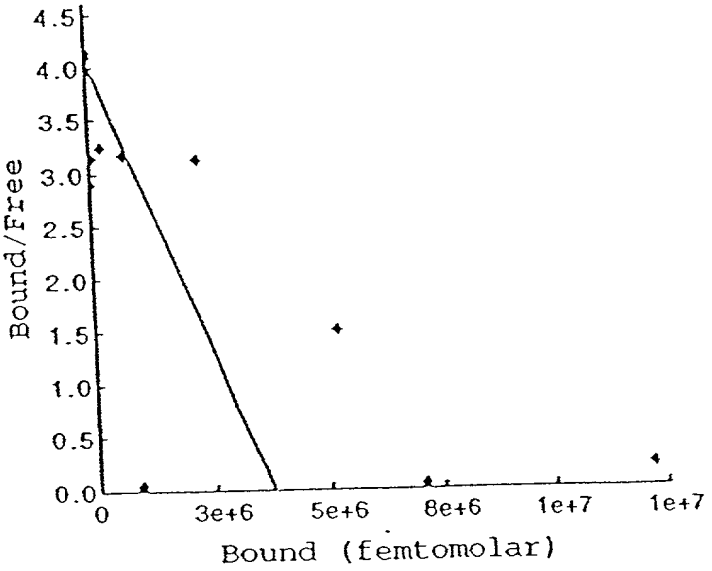


FIGURE 10 C

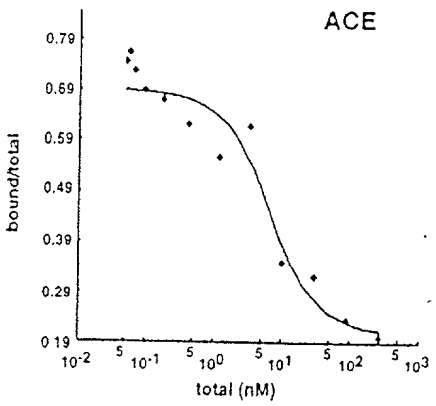

ACE
bound/total
0.79
0.69
0.59
0.49
0.39
0.29
0.19
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
total (nM)

FIGURE 11 C

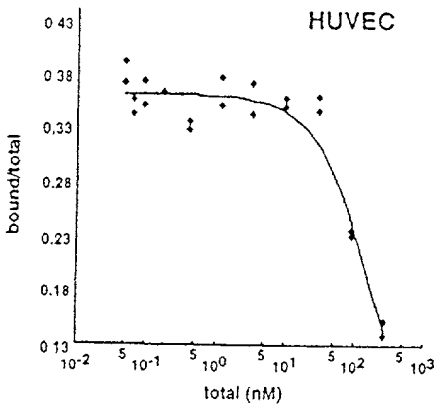

HUVEC
0 43
0 38
0,33
0.28
0.23
0.18
0 13
bound/total
10-2
10-1
100
101
102
103
total (nM)

FIGURE 12 A

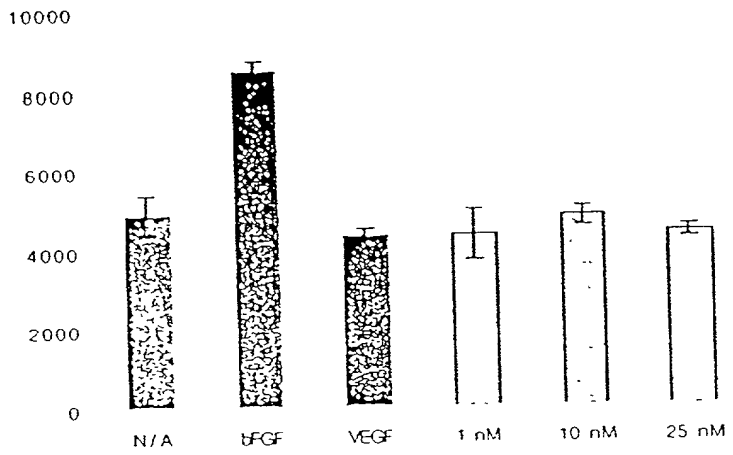
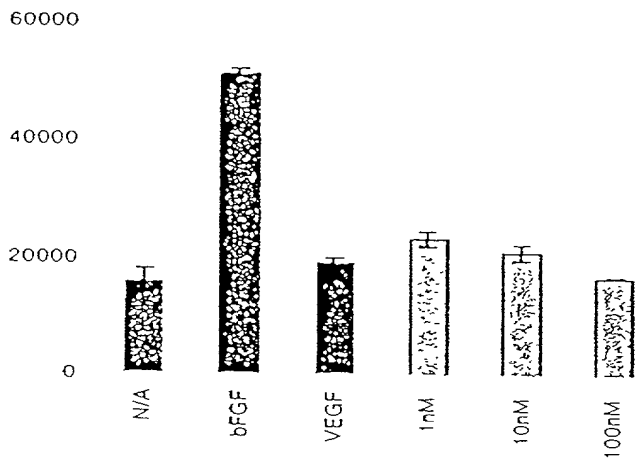


FIGURE 12 B



Case: GENENT.1516CP1
Applicant: Napoleone Ferrara, Colin Watanabe, William I. Wood and Theresa Shek
For: EG-VEGF ACIDS AND POLYPEPTIDES AND METHODS OF USE
Sheet 24 of 59 drawings

Ginger R. Dreger
KNOBBE, MARTENS, OLSON & BEAR, LLP
620 Newport Center Drive
Sixteenth Floor
Newport Beach, California 92660
(415) 954-4114

FIGURE 12 D

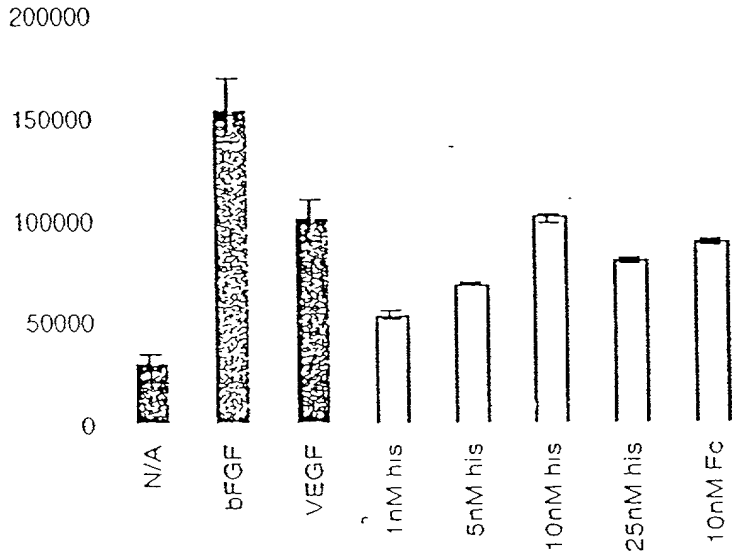
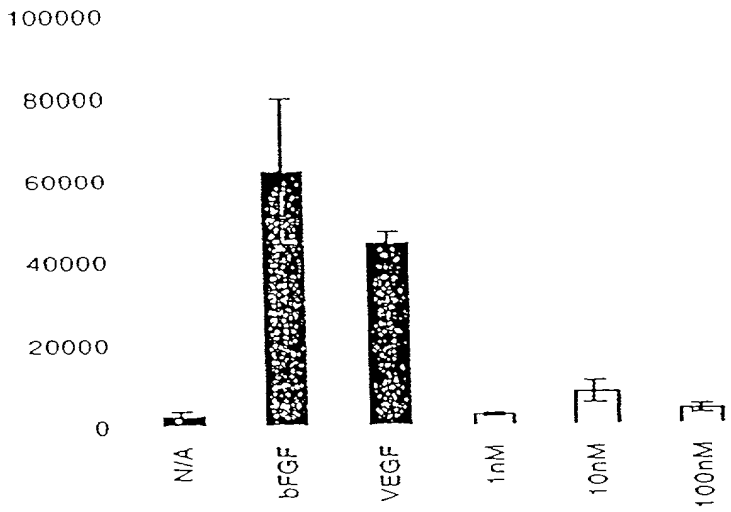

200000
150000
100000
50000
0
N/A
bFGF
VEGF
1nM his
5nM his
10nM his
25nM his
10nM Fc

FIGURE 12 E



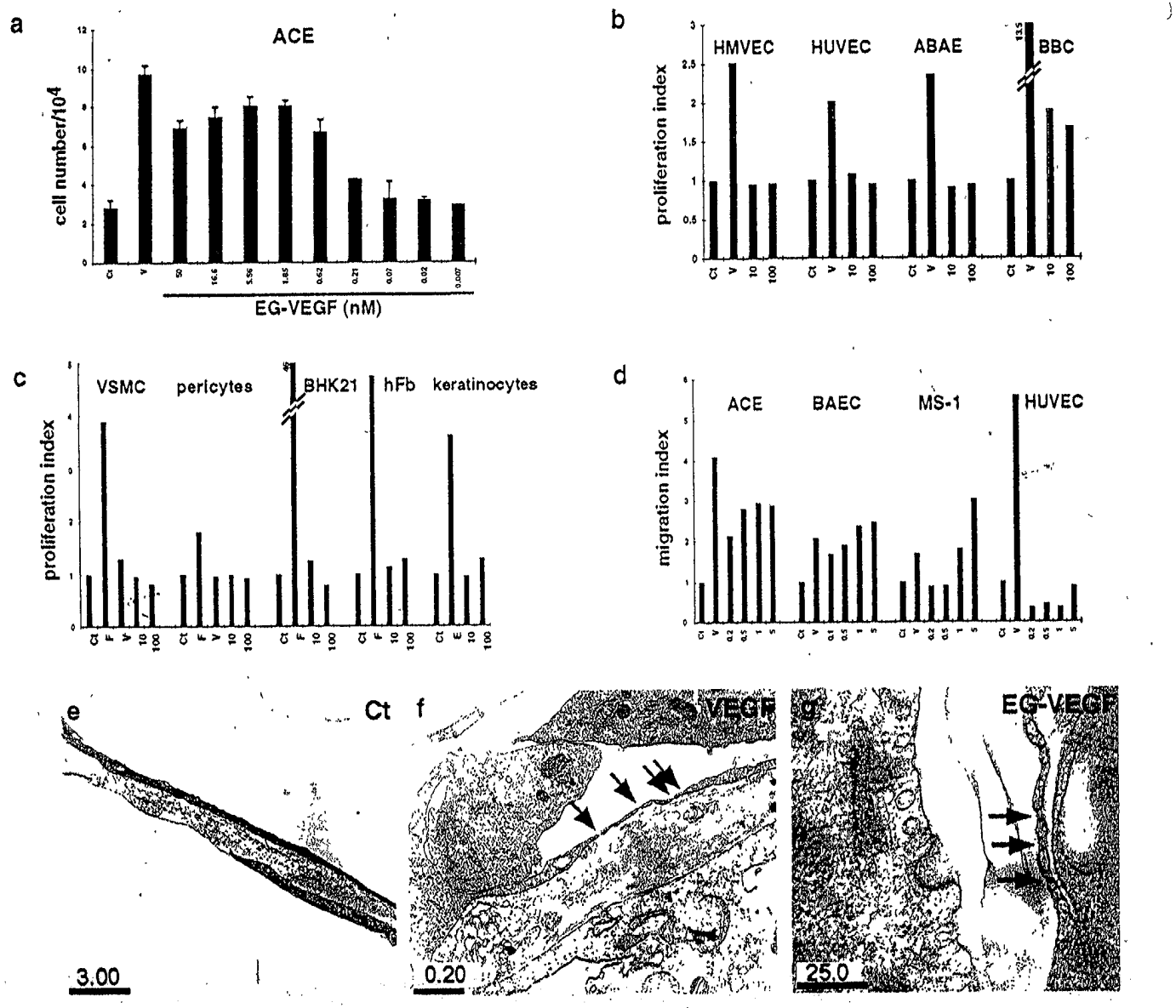


FIGURE 13

10027603 . 121901

FIGURE 14 A

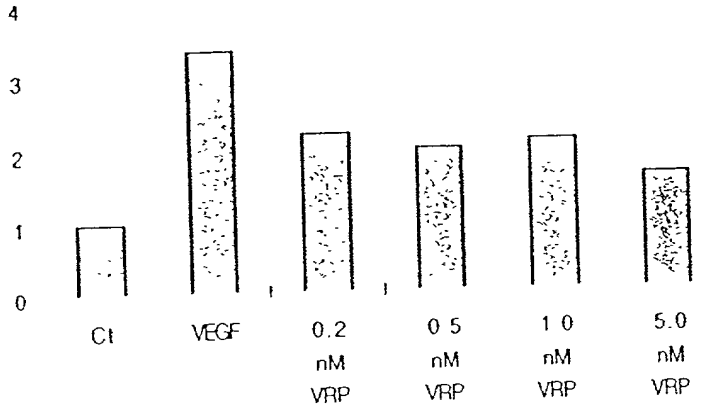


FIGURE 14 B

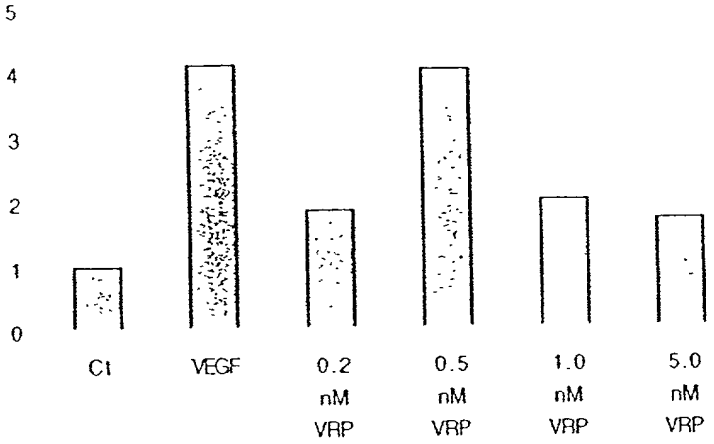


FIGURE 15

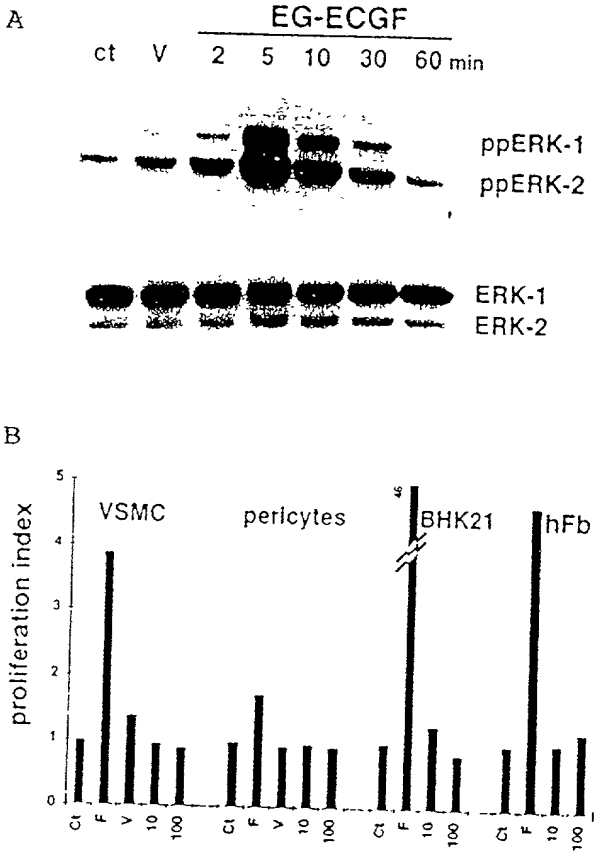

A
EG-ECGF
ct V 2 5 10 30 60 min
ppERK-1
ppERK-2
ERK-1
ERK-2
B
proliferation index
VSMC
pericytes
BHK21
hFb
Ct F V 10 100
Ct F V 10 100
Ct F 10 100
Ct F 10 100

FIGURE 16 A-C

a

```
TGGCCTCCCCAGCTTGCCAGGCACAAGGCTGAGCGGGAGGAAGCGAGAGG     50
CATCTAAGCAGGCAGTGTTTTGCCTTCACCCCAAGTGACCATGAGAGGTG
                                                 M  R  G
CCACGCGAGTCTCAATCATGCTCCTCCTAGTAACTGTGTCTGACTGTGCT
A  T  R  V  S  I  M  L  L  L  V  T  V  S  D  C  A
GTGATCACAGGGGCCTGTGAGCGGGATGTCCAGTGTGGGGCAGGCACCTG    200
 V  I  T  G  A  C  E  R  D  V  Q  C  G  A  G  T  C
CTGTGCCATCAGCCTGTGGCTTCGAGGGCTGCGGATGTGCACCCCGCTGG
  C  A  I  S  L  W  L  R  G  L  R  M  C  T  P  L
GGCGGGAAGGCGAGGAGTGCCACCCCGGCAGCCACAAGGTCCCCTTCTTC
G  R  E  G  E  E  C  H  P  G  S  H  K  V  P  F  F
AGGAAACGCAAGCACCACACCTGTCCTTGCTTGCCCAACCTGCTGTGCTC
 R  K  R  K  H  H  T  C  P  C  L  P  N  L  L  C  S
CAGGTTCCCGGACGGCAGGTACCGCTGCTCCATGGACTTGAAGAACATCA    400
  R  F  P  D  G  R  Y  R  C  S  M  D  L  K  N  I
ATTTTTAGGCGCTTGCCTGGTCTCAGGATACCCACCATCCTTTTCCTGAG
N  F  *
CACAGCCTGGATTTTTATTTCTGCCATGAAACCCAGCTCCCATGACTCTC
CCAGTCCCTACACTGACTACCCTGATCTCTCTTGTCTAGTACGCACATAT
GCACACAGGCAGACATACCTCCCATCATGACATGGTCCCCAGGCTGGCCT    600
GAGGATGTCACAGCTTGAGGCTGTGGTGTGAAAGGTGGCCAGCCTGGTTC
TCTTCCCTGCTCAGGCTGCCAGAGAGGTGGTAAATGGCAGAAAGGACATT
CCCCCTCCCCTCCCCAGGTGACCTGCTCTCTTTCCTGGGCCCTGCCCCTC
TCCCCACATGTATCCCTCGGTCTGAATTAGACATTCCTGGGCACAGGCTC    800
TTGGGTGCATTGCTCAGAGTCCCAGGTCCTGGCCTGACCCTCAGGCCCTT
CACGTGAGGTCTGTGAGGACCAATTTGTGGGTAGTTCATCTTCCCTCGAT
TGGTTAACTCCTTAGTTTCAGACCACAGACTCAAGATTGGCTCTTCCCAG
AGGGCAGCAGACAGTCACCCCAAGGCAGGTGTAGGGAGCCCAGGGAGGCC   1000
AATCAGCCCCCTGAAGACTCTGGTCCCAGTCAGCCTGTGGCTTGTGGCCT
GTGACCTGTGACCTTCTGCCAGAATTGTCATGCCTCTGAGGCCCCCTCTT
ACCACACTTTACCAGTTAACCACTGAAGCCCCCAATTCCCACAGCTTTTC
CATTAAAATGCAAATGGTGGTGGTTCAATCTAATCTGATATTGACATATT   1200
AGAAGGCAATTAGGGTGTTTCCTTAAACAACTCCTTTCCAAGGATCAGCC
CTGAGAGCAGGTTGGTGACTTTGAGGAGGGCAGTCCTCTGTCCAGATTGG
GGTGGGAGCAAGGGACAGGGAGCAGGGCAGGGGCTGAAAGGGGCACTGAT
TCAGACCAGGGAGGCAACTACACACCAACATGCTGGCTTTAGAATAAAAG   1400
CACCAACTGAAAAAA
```

b

```
MRGATRVSIMLLLVTVSDCAVITGACERDVQCGAGTCCATSLWLRGLRMC   50  EG-VEGF
MLLLLLLLPPLLLPRAGDAAVITGACDKDSQCGGGMCCAVSIWVKSIRIC   48  Bv8 hom
                    AVITGACERDLQCGKGTCCAVSLWIKSVRVC   31  VPRA

TPLGREGEECHPGSHKVPFFRKRKKHHTCPCLPNLLCSREEDGRYRCSMDL  100  EG-VEGF
TPMGKLGDSCHPLTRKVPFFGRRMHHTCPCLPGLACLRTSFNRFICLAQK   95  Bv8 hom
TPVGTSGEDCHPASHKTPFSGQRMHHTCPCAPNLACVGTEK-REKCLSK    79  VPRA

KNINF  105  EG-VEGF
```

c

```
CERDVQCGAGTCCATSLWLRGLR--MCTPLGREGEEC--HPGSHKVPFF   70  EG-VEGF
CDNQRDCQPGLCCAFQ---RGLLFPVCTPLPVEGELC--HDPASRLLDLI  252  hdkk3
CLRSTDCAPGLCCA-----EHFWSKICKPVLDEGQVCTKHRRKGS-----  215  xdkk1
CLNSADCKSN-CCHDTIISLSR---CALKARFNSECSAFTLYG------  55  col

RKRKH-----HTCPCLPNLLCSR---------FPDGRYRCSMDLKNINF  105  EG-VEGF
TWELEPDGALDRCPCASGLLCQP--------HSHSLVYVCKPTFVG      290  hdkk3
-HGLE---IFQRCHCGAGLSCRLQKGEFTTVPKTSRLHTCQRH        254  xdkk1
--------VYYKCPCERGLTCEGDKSLV-GSITNTNFGICHDVGRSSD   94  col
```

FIGURE 17 A

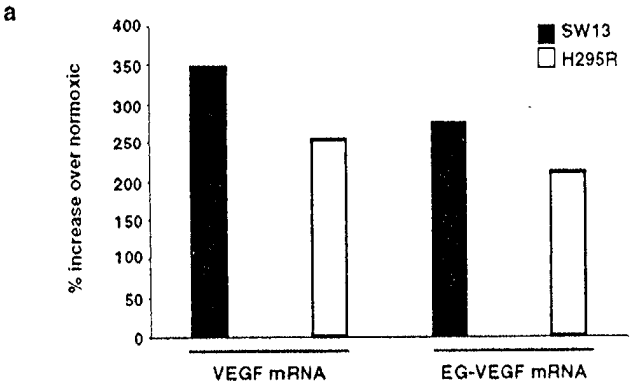
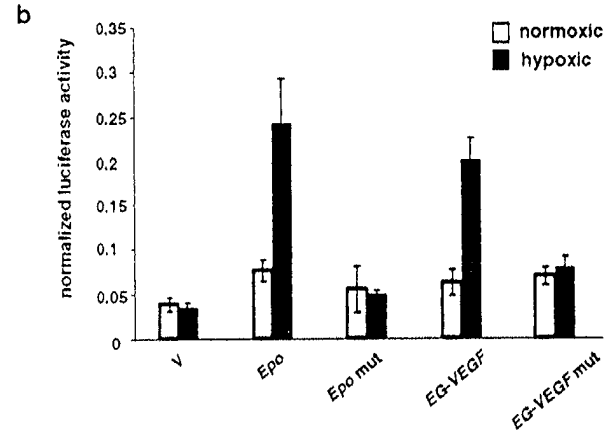


FIGURE 17 B



AGGCCCTACGTGCGGCCTCACACAGCCTGTTCTGA *Epo* SEQ ID NO: 16
AGGCCCTAATTGCGGCCTCACACAGCCTGTTCTGA *Epo* mut SEQ ID NO: 15
GCTAAGGACGTGCTATTCATGGGGTGCAGGAAGAT *EG-VEGF* SEQ ID NO: 17
GCTAAGGAATTGCTATTCATGGGGTGCAGGAAGAT *EG-VEGF* mut SEQ ID NO: 18

10029603.121901

FIGURE 18

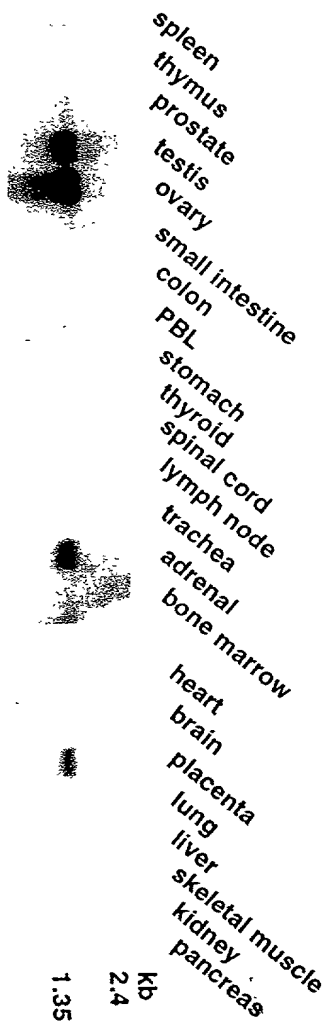

spleen
thymus
prostate
testis
ovary
small intestine
colon
PBL
stomach
thyroid
spinal cord
lymph node
trachea
adrenal
bone marrow
heart
brain
placenta
lung
liver
skeletal muscle
kidney
pancreas
kb
2.4
1.35

FIGURE 19 A-N


a
Ct
b
VEGF
c
EG-VEGF
d
lacZ
e
VEGF
f
EG-VEGF
sm
sm
sm
g
VEGF
h
EG-VEGF
i
Ct
VEGF
EG-VEGF
ov
ear
ear
j
lacZ
k
VEGF
l
EG-VEGF
CL
CL
CL
m
n
EG-VEGF

FIGURE 20 A

```
/*
 *
 * C-C increased from 12 to 15
 * Z is average of EQ
 * B is average of ND
 * match with stop is _M; stop-stop = 0; J (joker) match = 0
 */
#define  _M      -8      /* value of a match with a stop */

int      _day[26][26] = {
/*    A  B  C  D  E  F  G  H  I  J  K  L  M  N  O  P  Q  R  S  T  U  V  W  X  Y  Z */
/* A */   { 2, 0,-2, 0, 0,-4, 1,-1,-1, 0,-1,-2,-1, 0,_M, 1, 0,-2, 1, 1, 0, 0,-6, 0,-3, 0},
/* B */   { 0, 3,-4, 3, 2,-5, 0, 1,-2, 0, 0,-3,-2, 2,_M,-1, 1, 0, 0, 0, 0,-2,-5, 0,-3, 1},
/* C */   {-2,-4,15,-5,-5,-4,-3,-3,-2, 0,-5,-6,-5,-4,_M,-3,-5,-4, 0,-2, 0,-2,-8, 0, 0,-5},
/* D */   { 0, 3,-5, 4, 3,-6, 1, 1,-2, 0, 0,-4,-3, 2,_M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 2},
/* E */   { 0, 2,-5, 3, 4,-5, 0, 1,-2, 0, 0,-3,-2, 1,_M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 3},
/* F */   {-4,-5,-4,-6,-5, 9,-5,-2, 1, 0,-5, 2, 0,-4,_M,-5,-5,-4,-3,-3, 0,-1, 0, 0, 7,-5},
/* G */   { 1, 0,-3, 1, 0,-5, 5,-2,-3, 0,-2,-4,-3, 0,_M,-1,-1,-3, 1, 0, 0,-1,-7, 0,-5, 0},
/* H */   {-1, 1,-3, 1, 1,-2,-2, 6,-2, 0, 0,-2,-2, 2,_M, 0, 3, 2,-1,-1, 0,-2,-3, 0, 0, 2},
/* I */   {-1,-2,-2,-2,-2, 1,-3,-2, 5, 0,-2, 2, 2,-2,_M,-2,-2,-2,-1, 0, 0, 4,-5, 0,-1,-2},
/* J */   { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */   {-1, 0,-5, 0, 0,-5,-2, 0,-2, 0, 5,-3, 0, 1,_M,-1, 1, 3, 0, 0, 0,-2,-3, 0,-4, 0},
/* L */   {-2,-3,-6,-4,-3, 2,-4,-2, 2, 0,-3, 6, 4,-3,_M,-3,-2,-3,-3,-1, 0, 2,-2, 0,-1,-2},
/* M */   {-1,-2,-5,-3,-2, 0,-3,-2, 2, 0, 0, 4, 6,-2,_M,-2,-1, 0,-2,-1, 0, 2,-4, 0,-2,-1},
/* N */   { 0, 2,-4, 2, 1,-4, 0, 2,-2, 0, 1,-3,-2, 2,_M,-1, 1, 0, 1, 0, 0,-2,-4, 0,-2, 1},
/* O */   {_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M, 0,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M},
/* P */   { 1,-1,-3,-1,-1,-5,-1, 0,-2, 0,-1,-3,-2,-1,_M, 6, 0, 0, 1, 0, 0,-1,-6, 0,-5, 0},
/* Q */   { 0, 1,-5, 2, 2,-5,-1, 3,-2, 0, 1,-2,-1, 1,_M, 0, 4, 1,-1,-1, 0,-2,-5, 0,-4, 3},
/* R */   {-2, 0,-4,-1,-1,-4,-3, 2,-2, 0, 3,-3, 0, 0,_M, 0, 1, 6, 0,-1, 0,-2, 2, 0,-4, 0},
/* S */   { 1, 0, 0, 0, 0,-3, 1,-1,-1, 0, 0,-3,-2, 1,_M, 1,-1, 0, 2, 1, 0,-1,-2, 0,-3, 0},
/* T */   { 1, 0,-2, 0, 0,-3, 0,-1, 0, 0, 0,-1,-1, 0,_M, 0,-1,-1, 1, 3, 0, 0,-5, 0,-3, 0},
/* U */   { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */   { 0,-2,-2,-2,-2,-1,-1,-2, 4, 0,-2, 2, 2,-2,_M,-1,-2,-2,-1, 0, 0, 4,-6, 0,-2,-2},
/* W */   {-6,-5,-8,-7,-7, 0,-7,-3,-5, 0,-3,-2,-4,-4,_M,-6,-5, 2,-2,-5, 0,-6,17, 0, 0,-6},
/* X */   { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */   {-3,-3, 0,-4,-4, 7,-5, 0,-1, 0,-4,-1,-2,-2,_M,-5,-4,-4,-3,-3, 0,-2, 0, 0,10,-4},
/* Z */   { 0, 1,-5, 2, 3,-5, 0, 2,-2, 0, 0,-2,-1, 1,_M, 0, 3, 0, 0, 0, 0,-2,-6, 0,-4, 4}
};
```

FIGURE 20 B

```
/*
 */
#include <stdio.h>
#include <ctype.h>

#define  MAXJMP          16      /* max jumps in a diag */
#define  MAXGAP          24      /* don't continue to penalize gaps larger than this */
#define  JMPS            1024    /* max jmps in an path */
#define  MX              4       /* save if there's at least MX-1 bases since last jmp */

#define  DMAT            3       /* value of matching bases */
#define  DMIS            0       /* penalty for mismatched bases */
#define  DINS0           8       /* penalty for a gap */
#define  DINS1           1       /* penalty per base */
#define  PINS0           8       /* penalty for a gap */
#define  PINS1           4       /* penalty per residue */

struct jmp {
        short           n[MAXJMP];      /* size of jmp (neg for dely) */
        unsigned short  x[MAXJMP];      /* base no. of jmp in seq x */
};                                      /* limits seq to 2^16 -1 */

struct diag {
        int             score;          /* score at last jmp */
        long            offset;         /* offset of prev block */
        short           ijmp;           /* current jmp index */
        struct jmp      jp;             /* list of jmps */
};

struct path {
        int     spc;            /* number of leading spaces */
        short   n[JMPS];/* size of jmp (gap) */
        int     x[JMPS];/* loc of jmp (last elem before gap) */
};

char            *ofile;                 /* output file name */
char            *namex[2];              /* seq names: getseqs() */
char            *prog;                  /* prog name for err msgs */
char            *seqx[2];               /* seqs: getseqs() */
int             dmax;                   /* best diag: nw() */
int             dmax0;                  /* final diag */
int             dna;                    /* set if dna: main() */
int             endgaps;                /* set if penalizing end gaps */
int             gapx, gapy;             /* total gaps in seqs */
int             len0, len1;             /* seq lens */
int             ngapx, ngapy;           /* total size of gaps */
int             smax;                   /* max score: nw() */
int             *xbm;                   /* bitmap for matching */
long            offset;                 /* current offset in jmp file */
struct  diag    *dx;                    /* holds diagonals */
struct  path    pp[2];                  /* holds path for seqs */
char            *calloc(), *malloc(), *index(), *strcpy();
char            *getseq(), *g_calloc();
```

FIGURE 20 C

```
/* Needleman-Wunsch alignment program
 *
 * usage: progs file1 file2
 *  where file1 and file2 are two dna or two protein sequences.
 *  The sequences can be in upper- or lower-case an may contain ambiguity
 *  Any lines beginning with ';', '>' or '<' are ignored
 *  Max file length is 65535 (limited by unsigned short x in the jmp struct)
 *  A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
 *  Output is in the file "align.out"
 *
 * The program may create a tmp file in /tmp to hold info about traceback.
 * Original version developed under BSD 4.3 on a vax 8650
 */
#include "nw.h"
#include "day.h"

static    _dbval[26] = {
        1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static    _pbval[26] = {
        1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
        128, 256, 0xFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
        1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
        1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

                                                                    main
main(ac, av)
        int     ac;
        char    *av[];
{
        prog = av[0];
        if (ac != 3) {
                fprintf(stderr,"usage: %s file1 file2\n", prog);
                fprintf(stderr,"where file1 and file2 are two dna or two protein sequences.\n");
                fprintf(stderr,"The sequences can be in upper- or lower-case\n");
                fprintf(stderr,"Any lines beginning with ';' or '<' are ignored\n");
                fprintf(stderr,"Output is in the file \"align.out\"\n");
                exit(1);
        }
        namex[0] = av[1];
        namex[1] = av[2];
        seqx[0] = getseq(namex[0], &len0);
        seqx[1] = getseq(namex[1], &len1);
        xbm = (dna)? _dbval : _pbval;

        endgaps = 0;                    /* 1 to penalize endgaps */
        ofile = "align.out";            /* output file */

        nw();           /* fill in the matrix, get the possible jmps */
        readjmps();     /* get the actual jmps */
        print();        /* print stats, alignment */

        cleanup(0);     /* unlink any tmp files */
}
```

FIGURE 20 D

```
/* do the alignment, return best score: main()
 * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
 * pro: PAM 250 values
 * When scores are equal, we prefer mismatches to any gap, prefer
 * a new gap to extending an ongoing gap, and prefer a gap in seqx
 * to a gap in seq y.
 */
nw()                                                                    nw
{
        char            *px, *py;       /* seqs and ptrs */
        int             *ndely, *dely;  /* keep track of dely */
        int             ndelx, delx;    /* keep track of delx */
        int             *tmp;           /* for swapping row0, row1 */
        int             mis;            /* score for each type */
        int             ins0, ins1;     /* insertion penalties */
        register        id;             /* diagonal index */
        register        ij;             /* jmp index */
        register        *col0, *col1;   /* score for curr, last row */
        register        xx, yy;         /* index into seqs */

        dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

        ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
        dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
        col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
        col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
        ins0 = (dna)? DINS0 : PINS0;
        ins1 = (dna)? DINS1 : PINS1;

        smax = -10000;
        if (endgaps) {
                for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
                        col0[yy] = dely[yy] = col0[yy-1] - ins1;
                        ndely[yy] = yy;
                }
                col0[0] = 0;            /* Waterman Bull Math Biol 84 */
        }
        else
                for (yy = 1; yy <= len1; yy++)
                        dely[yy] = -ins0;

        /* fill in match matrix
         */
        for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
                /* initialize first entry in col
                 */
                if (endgaps) {
                        if (xx == 1)
                                col1[0] = delx = -(ins0+ins1);
                        else
                                col1[0] = delx = col0[0] - ins1;
                        ndelx = xx;
                }
                else {
                        col1[0] = 0;
                        delx = -ins0;
                        ndelx = 0;
                }
```

Patent Application Publication

FIGURE 20 E


```
for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
        mis = col0[yy-1];
        if (dna)
                mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
        else
                mis += _day[*px-'A'][*py-'A'];

        /* update penalty for del in x seq;
         * favor new del over ongong del
         * ignore MAXGAP if weighting endgaps
         */
        if (endgaps || ndely[yy] < MAXGAP) {
                if (col0[yy] - ins0 >= dely[yy]) {
                        dely[yy] = col0[yy] - (ins0+ins1);
                        ndely[yy] = 1;
                } else {
                        dely[yy] -= ins1;
                        ndely[yy]++;
                }
        } else {
                if (col0[yy] - (ins0+ins1) >= dely[yy]) {
                        dely[yy] = col0[yy] - (ins0+ins1);
                        ndely[yy] = 1;
                } else
                        ndely[yy]++;
        }

        /* update penalty for del in y seq;
         * favor new del over ongong del
         */
        if (endgaps || ndelx < MAXGAP) {
                if (col1[yy-1] - ins0 >= delx) {
                        delx = col1[yy-1] - (ins0+ins1);
                        ndelx = 1;
                } else {
                        delx -= ins1;
                        ndelx++;
                }
        } else {
                if (col1[yy-1] - (ins0+ins1) >= delx) {
                        delx = col1[yy-1] - (ins0+ins1);
                        ndelx = 1;
                } else
                        ndelx++;
        }

        /* pick the maximum score; we're favoring
         * mis over any del and delx over dely
         */
```

FIGURE 20 F


```
                id = xx - yy + len1 - 1;
                if (mis >= delx && mis >= dely[yy])
                        col1[yy] = mis;
                else if (delx >= dely[yy]) {
                        col1[yy] = delx;
                        ij = dx[id].ijmp;
                        if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
                        && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
                                dx[id].ijmp++;
                                if (++ij >= MAXJMP) {
                                        writejmps(id);
                                        ij = dx[id].ijmp = 0;
                                        dx[id].offset = offset;
                                        offset += sizeof(struct jmp) + sizeof(offset);
                                }
                        }
                        dx[id] jp.n[ij] = ndelx;
                        dx[id] jp.x[ij] = xx;
                        dx[id].score = delx;
                }
                else {
                        col1[yy] = dely[yy];
                        ij = dx[id] ijmp;

if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
                        && xx > dx[id].jp.x[ij]+MX) || mis > dx[id] score+DINS0)) {
                                dx[id].ijmp++;
                                if (++ij >= MAXJMP) {
                                        writejmps(id);
                                        ij = dx[id].ijmp = 0,
                                        dx[id].offset = offset;
                                        offset += sizeof(struct jmp) + sizeof(offset),
                                }
                        }
                        dx[id] jp.n[ij] = -ndely[yy],
                        dx[id] jp.x[ij] = xx;
                        dx[id].score = dely[yy];
                }
                if (xx == len0 && yy < len1) {
                        /* last col
                         */
                        if (endgaps)
                                col1[yy] -= ins0+ins1*(len1-yy);
                        if (col1[yy] > smax) {
                                smax = col1[yy];
                                dmax = id;
                        }
                }
        }
        if (endgaps && xx < len0)
                col1[yy-1] -= ins0+ins1*(len0-xx);
        if (col1[yy-1] > smax) {
                smax = col1[yy-1];
                dmax = id;
        }
        tmp = col0; col0 = col1; col1 = tmp;
}
(void) free((char *)ndely);
(void) free((char *)dely);
(void) free((char *)col0);
(void) free((char *)col1);}
```

FIGURE 20 G

```
/*
 *
 * print() -- only routine visible outside this module
 *
 * static:
 * getmat() -- trace back best path, count matches: print()
 * pr_align() -- print alignment of described in array p[]: print()
 * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
 * nums() -- put out a number line. dumpblock()
 * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 * stars() - -put a line of stars. dumpblock()
 * stripname() -- strip any path and prefix from a seqname
 */

#include "nw.h"

#define SPC     3
#define P_LINE  256     /* maximum output line */
#define P_SPC   3       /* space between name or num and seq */

extern  _day[26][26];
int     olen;           /* set output line length */
FILE    *fx,            /* output file */

print()
{
        int     lx, ly, firstgap, lastgap;      /* overlap */

        if ((fx = fopen(ofile, "w")) == 0) {
                fprintf(stderr,"%s: can't write %s\n", prog, ofile);
                cleanup(1),
        }
        fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
        fprintf(fx, "<second sequence· %s (length = %d)\n", namex[1], len1);
        olen = 60;
        lx = len0;
        ly = len1,
        firstgap = lastgap = 0,
        if (dmax < len1 - 1) {          /* leading gap in x */
                pp[0] spc = firstgap = len1 - dmax - 1;
                ly -= pp[0] spc;
        }
        else if (dmax > len1 - 1) {     /* leading gap in y */
                pp[1] spc = firstgap = dmax - (len1 - 1);
                lx -= pp[1] spc;
        }
        if (dmax0 < len0 - 1) {         /* trailing gap in x */
                lastgap = len0 - dmax0 -1;
                lx -= lastgap;
        }
        else if (dmax0 > len0 - 1) {    /* trailing gap in y */
                lastgap = dmax0 - (len0 - 1);
                ly -= lastgap,
        }
        getmat(lx, ly, firstgap, lastgap);
        pr_align();
}
```

print

FIGURE 20 H

```
/*
 * trace back the best path, count matches
 */
static
getmat(lx, ly, firstgap, lastgap)                                        getmat
        int     lx, ly;                 /* "core" (minus endgaps) */
        int     firstgap, lastgap;      /* leading trailing overlap */
{
        int             nm, i0, i1, siz0, siz1;
        char            outx[32];
        double          pct;
        register        n0, n1;
        register char   *p0, *p1;

        /* get total matches, score
         */
        i0 = i1 = siz0 = siz1 = 0;
        p0 = seqx[0] + pp[1] spc;
        p1 = seqx[1] + pp[0].spc;
        n0 = pp[1].spc + 1;
        n1 = pp[0].spc + 1;

        nm = 0;
        while ( *p0 && *p1 ) {
                if (siz0) {
                        p1++;
                        n1++;
                        siz0--;
                }
                else if (siz1) {
                        p0++;
                        n0++;
                        siz1--;
                }
                else {
                        if (xbm[*p0-'A']&xbm[*p1-'A'])
                                nm++;
                        if (n0++ == pp[0].x[i0])
                                siz0 = pp[0].n[i0++];
                        if (n1++ == pp[1].x[i1])
                                siz1 = pp[1].n[i1++];
                        p0++;
                        p1++;
                }
        }

        /* pct homology:
         * if penalizing endgaps, base is the shorter seq
         * else, knock off overhangs and take shorter core
         */
        if (endgaps)
                lx = (len0 < len1)? len0 : len1;
        else
                lx = (lx < ly)? lx : ly;
        pct = 100.*(double)nm/(double)lx;
        fprintf(fx, "\n");
        fprintf(fx, "<%d match%s in an overlap of %d: %.2f percent similarity\n",
                nm, (nm == 1)? "" : "es", lx, pct);
```

FIGURE 20 I

```
        fprintf(fx, "<gaps in first sequence: %d", gapx);                    ...getmat
        if (gapx) {
                (void) sprintf(outx, " (%d %s%s)",
                        ngapx, (dna)? "base":"residue", (ngapx == 1)? "":"s");
                fprintf(fx,"%s", outx);

        fprintf(fx, ", gaps in second sequence: %d", gapy);
        if (gapy) {
                (void) sprintf(outx, " (%d %s%s)",
                        ngapy, (dna)? "base"."residue", (ngapy == 1)? "":"s");
                fprintf(fx,"%s", outx);
        }
        if (dna)
                fprintf(fx,
                "\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
                smax, DMAT, DMIS, DINS0, DINS1);
        else
                fprintf(fx,
                "\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
                smax, PINS0, PINS1);
        if (endgaps)
                fprintf(fx,
                "<endgaps penalized  left endgap: %d %s%s, right endgap: %d %s%s\n",
                firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
                lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
        else
                fprintf(fx, "<endgaps not penalized\n");
}

static          nm,             /* matches in core -- for checking */
static          lmax,           /* lengths of stripped file names */
static          ij[2],          /* jmp index for a path */
static          nc[2],          /* number at start of current line */
static          ni[2],          /* current elem number -- for gapping */
static          siz[2],
static char     *ps[2],         /* ptr to current element */
static char     *po[2],         /* ptr to next output char slot */
static char     out[2][P_LINE], /* output line */
static char     star[P_LINE];   /* set by stars() */

/*
* print alignment of described in struct path pp[]
 */
static
pr_align()                                                           pr_align
{
        int             nn,     /* char count */
        int             more;
        register        i;

        for (i =  0, lmax = 0; i < 2; i++) {
                nn = stripname(namex[i]),
                if (nn > lmax)
                        lmax = nn,

                nc[i] = 1;
                ni[i] = 1;
                siz[i] = ij[i] = 0;
                ps[i] = seqx[i];
                po[i] = out[i],
        }
        Page 3 of nwprint c
```

FIGURE 20 J

```
        for (nn = nm = 0, more = 1; more; ) {                                   ...pr_align
                for (i = more = 0, i < 2, i++) {
                        /*
                         * do we have more of this sequence?
                         */
                        if (!*ps[i])
                                continue,

                        more++;

                        if (pp[i] spc) {        /* leading space */
                                *po[i]++ = ' ';
                                pp[i].spc--,
                        }
                        else if (siz[i]) {      /* in a gap */
                                *po[i]++ = '-',
                                siz[i]--;
                        }
                        else {                  /* we're putting a seq element
                                                 */
                                *po[i] = *ps[i],
                                if (islower(*ps[i]))
                                        *ps[i] = toupper(*ps[i]),
                                po[i]++,
                                ps[i]++,

                                /*
                                 * are we at next gap for this seq?
                                 */
                                if (ni[i] == pp[i] x[ij[i]]) {
                                        /*
                                         * we need to merge all gaps
                                         * at this location
                                         */
                                        siz[i] = pp[i] n[ij[i]++],
                                        while (ni[i] == pp[i] x[ij[i]])
                                                siz[i] += pp[i] n[ij[i]++],
                                }
                                ni[i]++;
                        }
                }
                if (++nn == olen || !more && nn) {
                        dumpblock(),
                        for (i = 0, i < 2, i++)
                                po[i] = out[i],
                        nn = 0;
                }
        }
}

/*
 * dump a block of lines, including numbers, stars: pr_align()
 */
static
dumpblock()                                                                     dumpblock
{
        register  i,

        for (i = 0, i < 2, i++)
                *po[i]-- = '\0';
```

FIGURE 20 K

...dumpblock

```
        (void) putc('\n', fx);
        for (i = 0, i < 2; i++) {
                if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
                        if (i == 0)
                                nums(i);
                        if (i == 0 && *out[1])
                                stars();
                        putline(i);
                        if (i == 0 && *out[1])
                                fprintf(fx, star);
                        if (i == 1)
                                nums(i);
                }
        }
}

/*
 * put out a number line: dumpblock()
 */
static
nums(ix)                                                                    nums
        int     ix,     /* index in out[] holding seq line */
{
        char            nline[P_LINE],
        register        i, j,
        register char   *pn, *px, *py;

        for (pn = nline, i = 0, i < lmax+P_SPC; i++, pn++)
                *pn = ' ';
        for (i = nc[ix], py = out[ix], *py, py++, pn++) {
                if (*py == ' ' || *py == '-')
                        *pn = ' ',
                else {
                        if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                                j = (i < 0)? -i : i,
                                for (px = pn; j; j /= 10, px--)
                                        *px = j%10 + '0';
                                if (i < 0)
                                        *px = '-';
                        }
                        else
                                *pn = ' ';
                        i++;
                }
        }
        *pn = '\0';
        nc[ix] = i,
        for (pn = nline; *pn; pn++)
                (void) putc(*pn, fx);
        (void) putc('\n', fx);
}

/*
 * put out a line (name, [num], seq, [num]). dumpblock()
 */
static
putline(ix)                                                                 putline
        int     ix;
{
```

FIGURE 20 L

...putline

```
        int             i;
        register char   *px;
        for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
                (void) putc(*px, fx);
        for (; i < lmax+P_SPC; i++)
                (void) putc(' ', fx);

        /* these count from 1:
         * ni[] is current element (from 1)
         * nc[] is number at start of current line
         */
        for (px = out[ix]; *px; px++)
                (void) putc(*px&0x7F, fx);
        (void) putc('\n', fx);
}


/*
 * put a line of stars (seqs always in out[0], out[1]): dumpblock()
 */
static
stars()                                                          stars
{
        int             i;
        register char   *p0, *p1, cx, *px;

        if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
           !*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
                return;
        px = star;
        for (i = lmax+P_SPC; i; i--)
                *px++ = ' ';

        for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
                if (isalpha(*p0) && isalpha(*p1)) {

                        if (xbm[*p0-'A']&xbm[*p1-'A']) {
                                cx = '*';
                                nm++;
                        }
                        else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
                                cx = '.';
                        else
                                cx = ' ';
                }
                else
                        cx = ' ';
                *px++ = cx;
        }
        *px++ = '\n';
        *px = '\0';
}
```

FIGURE 20 M

```
/*
 * strip path or prefix from pn, return len: pr_align()
 */
static
stripname(pn)                                                          stripname
        char    *pn;    /* file name (may be path) */
{
        register char   *px, *py;

        py = 0;
        for (px = pn; *px; px++)
                if (*px == '/')
                        py = px + 1;
        if (py)
                (void) strcpy(pn, py);
        return(strlen(pn));

}
```


EXHIBIT 1030

FIGURE 20 N

```
/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
 * g_calloc() -- calloc() with error checkin
 * readjmps() -- get the good jmps, from tmp file if necessary
 * writejmps() -- write a filled array of jmps to a tmp file: nw()
 */
#include "nw.h"
#include <sys/file.h>

char    *jname = "/tmp/homgXXXXXX";             /* tmp file for jmps */
FILE    *fj;

int     cleanup(),                              /* cleanup tmp file */
long    lseek(),

/*
 * remove any tmp file if we blow
 */                                                                     cleanup
cleanup(i)
        int     i;
{
        if (fj)
                (void) unlink(jname),
        exit(i),
}

/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
char    *
getseq(file, len)                                                       getseq
        char    *file,  /* file name */
        int     *len;   /* seq len */
{
        char            line[1024], *pseq;
        register char   *px, *py;
        int             natgc, tlen;
        FILE            *fp;

        if ((fp = fopen(file,"r")) == 0) {
                fprintf(stderr,"%s: can't read %s\n", prog, file),
                exit(1),
        }
        tlen = natgc = 0,
        while (fgets(line, 1024, fp)) {
                if (*line == ';' || *line == '<' || *line == '>')
                        continue;
                for (px = line; *px != '\n'; px++)
                        if (isupper(*px) || islower(*px))
                                tlen++;
        }
        if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
                fprintf(stderr,"%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
                exit(1),
        }
        pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';
```

FIGURE 20 O

...getseq

```
        py = pseq + 4;
        *len = tlen,
        rewind(fp),

        while (fgets(line, 1024, fp)) {
                if (*line == ';' || *line == '<' || *line == '>')
                        continue;
                for (px = line, *px != '\n', px++) {
                        if (isupper(*px))
                                *py++ = *px,
                        else if (islower(*px))
                                *py++ = toupper(*px),
                        if (index("ATGCU",*(py-1)))
                                natgc++,
                }
        }
        *py++ = '\0';
        *py = '\0';
        (void) fclose(fp),
        dna = natgc > (tlen/3);
        return(pseq+4),
}

char    *
g_calloc(msg, nx, sz)                                                   g_calloc
        char    *msg,           /* program, calling routine */
        int     nx, sz,         /* number and size of elements */
{
        char            *px, *calloc();

        if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
                if (*msg) {
                        fprintf(stderr, "%s  g_calloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz),
                        exit(1),
                }
        }
        return(px),
}

/*
 * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
 */
readjmps()                                                              readjmps
{
        int             fd = -1;
        int             siz, i0, i1,
        register  i, j, xx,

        if (fj) {
                (void) fclose(fj);
                if ((fd = open(jname, O_RDONLY, 0)) < 0) {
                        fprintf(stderr, "%s: can't open() %s\n", prog, jname);
                        cleanup(1);
                }
        }
        for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
                while (1) {
                        for (j = dx[dmax] ijmp; j >= 0 && dx[dmax] jp.x[j] >= xx; j--)
                                ;
```

FIGURE 20 P


```
                        if (j < 0 && dx[dmax] offset && fj) {
                                (void) lseek(fd, dx[dmax].offset, 0);
                                (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
                                (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax] offset));
                                dx[dmax] ijmp = MAXJMP-1;
                        }
                        else
                                break;
                }
                if (i >= JMPS) {
                        fprintf(stderr, "%s: too many gaps in alignment\n", prog);
                        cleanup(1);
                }
                if (j >= 0) {
                        siz = dx[dmax] jp n[j];
                        xx = dx[dmax].jp x[j];
                        dmax += siz;
                        if (siz < 0) {                  /* gap in second seq */
                                pp[1] n[i1] = -siz;
                                xx += siz;
                                /* id = xx - yy + len1 - 1
                                 */
                                pp[1].x[i1] = xx - dmax + len1 - 1;
                                gapy++;
                                ngapy -= siz;
/* ignore MAXGAP when doing endgaps */
                                siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
                                i1++;
                        }
                        else if (siz > 0) {     /* gap in first seq */
                                pp[0] n[i0] = siz;
                                pp[0] x[i0] = xx;
                                gapx++;
                                ngapx += siz;
/* ignore MAXGAP when doing endgaps */
                                siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
                                i0++;
                        }
                }
                else
                        break;
        }
        /* reverse the order of jmps
         */
        for (j = 0, i0--; j < i0; j++, i0--) {
                i = pp[0] n[j]; pp[0] n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
                i = pp[0].x[j]; pp[0].x[j] = pp[0] x[i0], pp[0] x[i0] = i;
        }
        for (j = 0, i1--; j < i1; j++, i1--) {
                i = pp[1].n[j]; pp[1] n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
                i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
        }
        if (fd >= 0)
                (void) close(fd);
        if (fj) {
                (void) unlink(jname);
                fj = 0;
                offset = 0;
        }
}
```

FIGURE 20 Q

```
/*
 * write a filled jmp struct offset of the prev one (if any): nw()
 */                                                                    writejmps
writejmps(ix)
        int     ix;
{
        char    *mktemp();

        if (!fj) {
                if (mktemp(jname) < 0) {
                        fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
                        cleanup(1);
                }
                if ((fj = fopen(jname, "w")) == 0) {
                        fprintf(stderr, "%s: can't write %s\n", prog, jname);
                        exit(1);
                }
        }
        (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
        (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
}
```

Page 4 of nwsubr.c

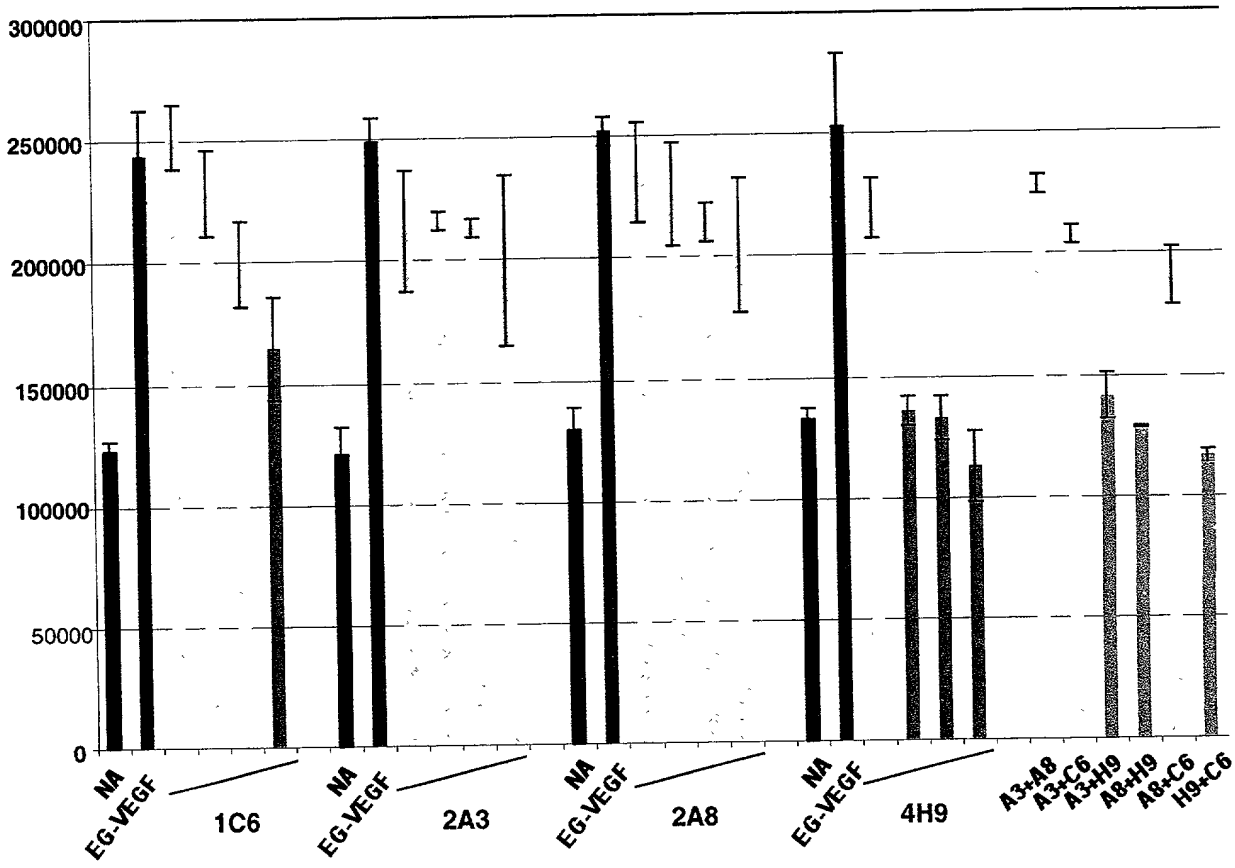

300000
250000
200000
150000
100000
50000
0
NA
EG-VEGF
1C6
NA
EG-VEGF
2A3
NA
EG-VEGF
2A8
NA
EG-VEGF
4H9
A3+A8
A3+C6
A3+H9
A8+H9
A8+C6
H9+C6

FIGURE 21

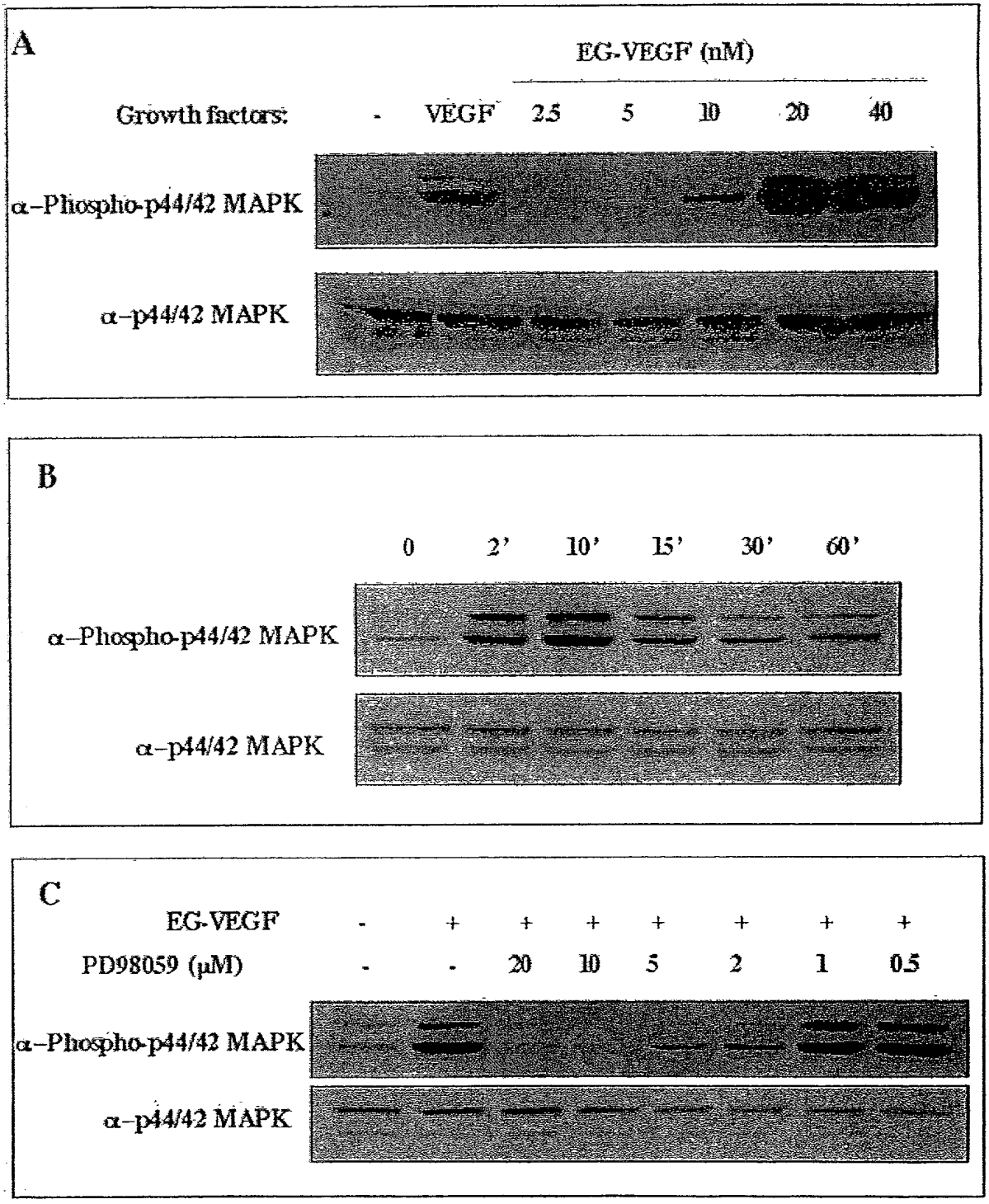

A
EG-VEGF (nM)
Growth factors:
-
VEGF
2.5
5
10
20
40
α–Phospho-p44/42 MAPK
α–p44/42 MAPK
B
0
2'
10'
15'
30'
60'
α–Phospho-p44/42 MAPK
α–p44/42 MAPK
C
EG-VEGF
PD98059 (μM)
α–Phospho-p44/42 MAPK
α–p44/42 MAPK

FIGURE 22

FIGURE 23

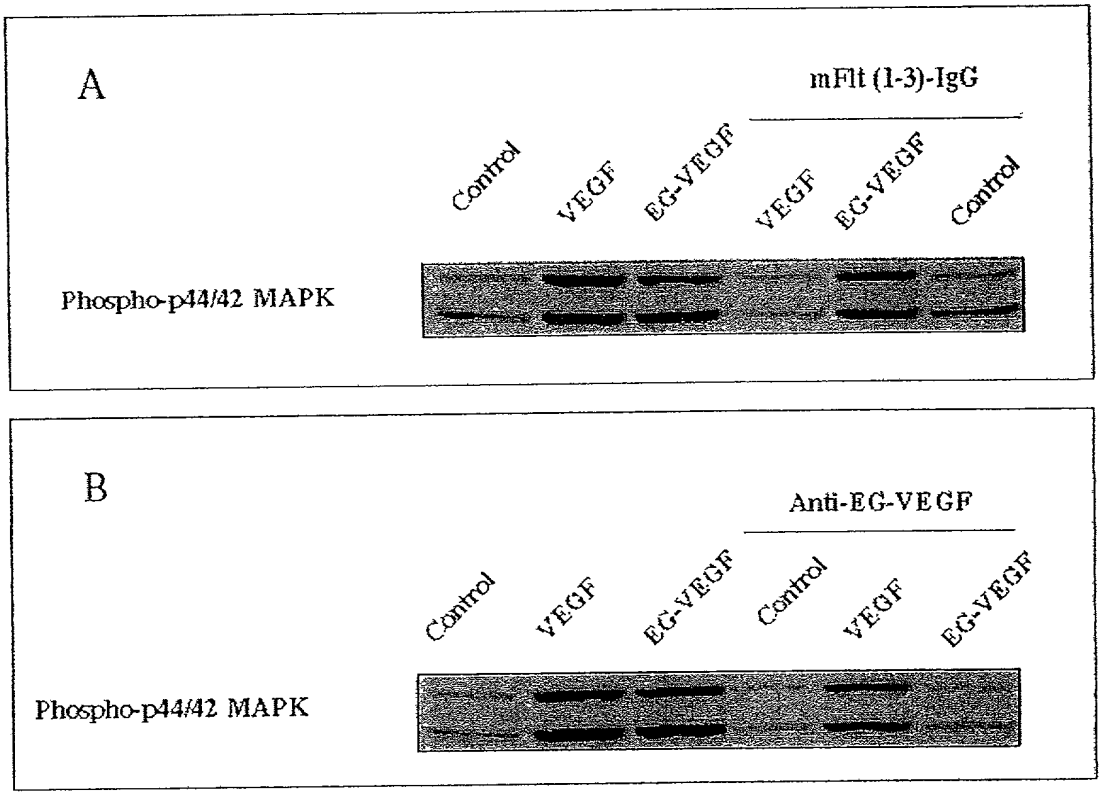

A
mFlt (1-3)-IgG
Control
VEGF
EG-VEGF
VEGF
EG-VEGF
Control
Phospho-p44/42 MAPK
B
Anti-EG-VEGF
Control
VEGF
EG-VEGF
Control
VEGF
EG-VEGF
Phospho-p44/42 MAPK

FIGURE 24

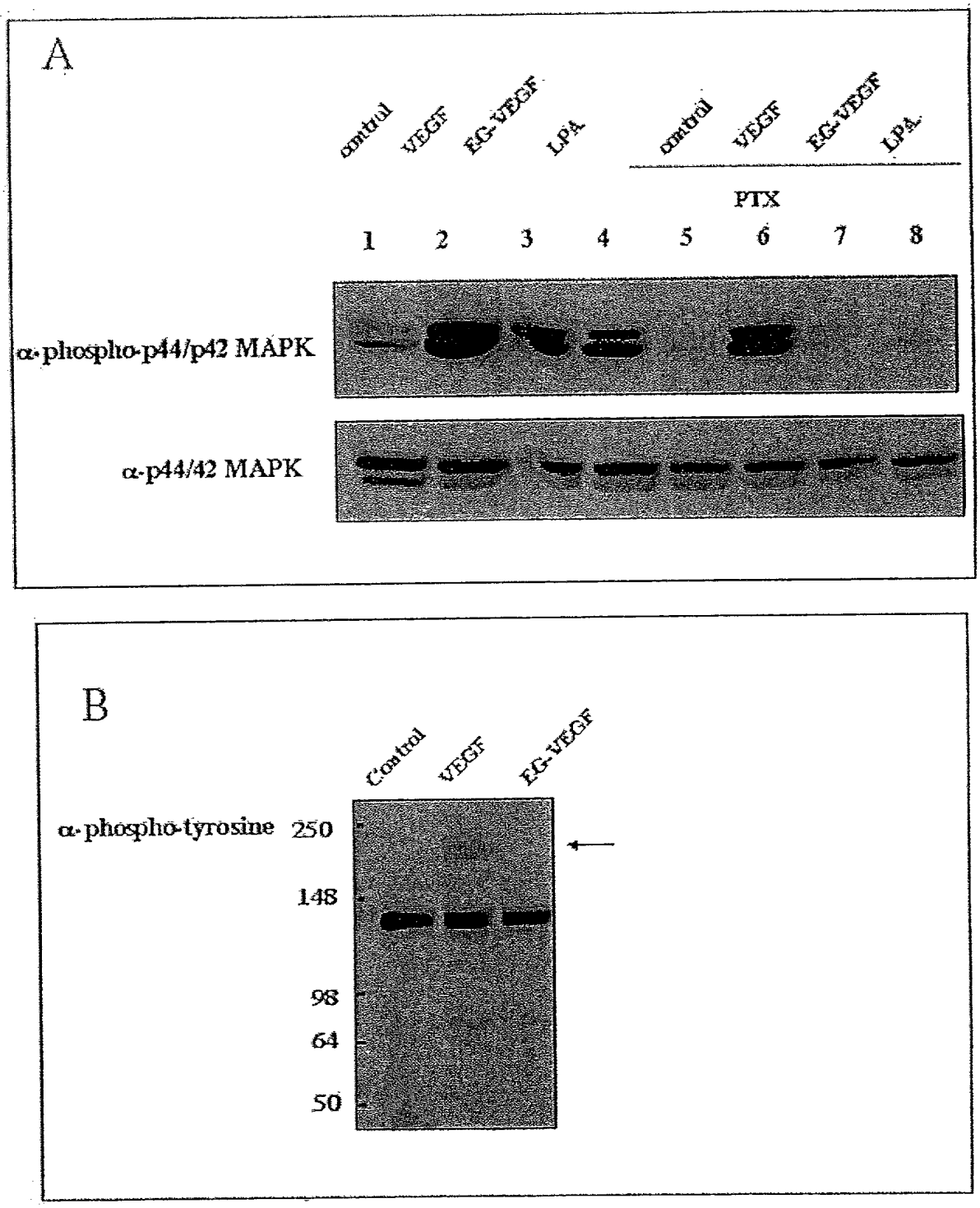

A
control
VEGF
EG-VEGF
LPA
control
VEGF
EG-VEGF
LPA
PTX
1 2 3 4 5 6 7 8
α-phospho-p44/p42 MAPK
α-p44/42 MAPK
B
Control
VEGF
EG-VEGF
α-phospho-tyrosine
250
148
98
64
50

FIGURE 25

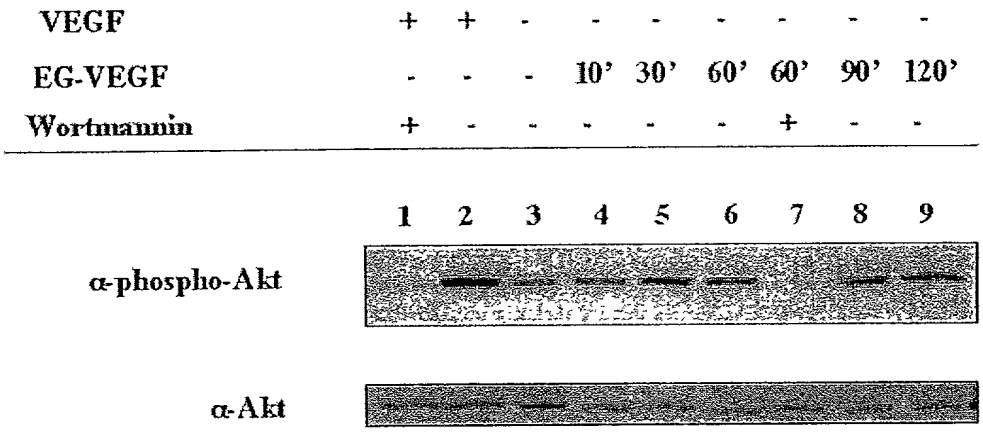
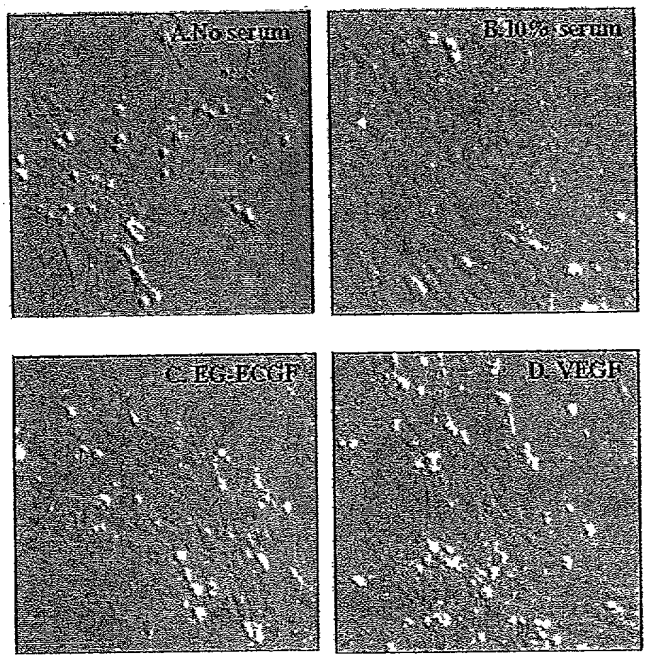

VEGF + + - - - - - - -
EG-VEGF - - - 10' 30' 60' 60' 90' 120'
Wortmannin + - - - - - + - -
1 2 3 4 5 6 7 8 9
α-phospho-Akt
α-Akt

FIGURE 26


A. No serum
B. 10% serum
C. EG-FCGF
D. VEGF

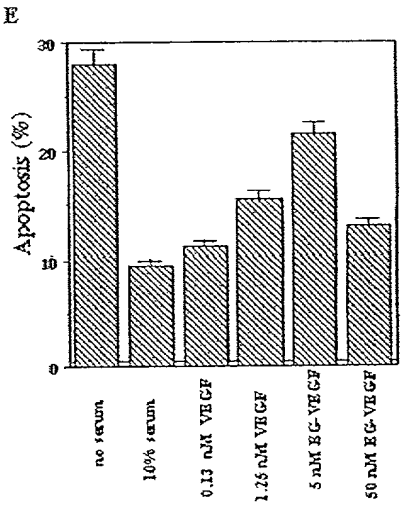

E
Apoptosis (%)
30
20
10
0
no serum
10% serum
0.13 nM VEGF
1.25 nM VEGF
5 nM EG-VEGF
50 nM EG-VEGF

FIGURE 27

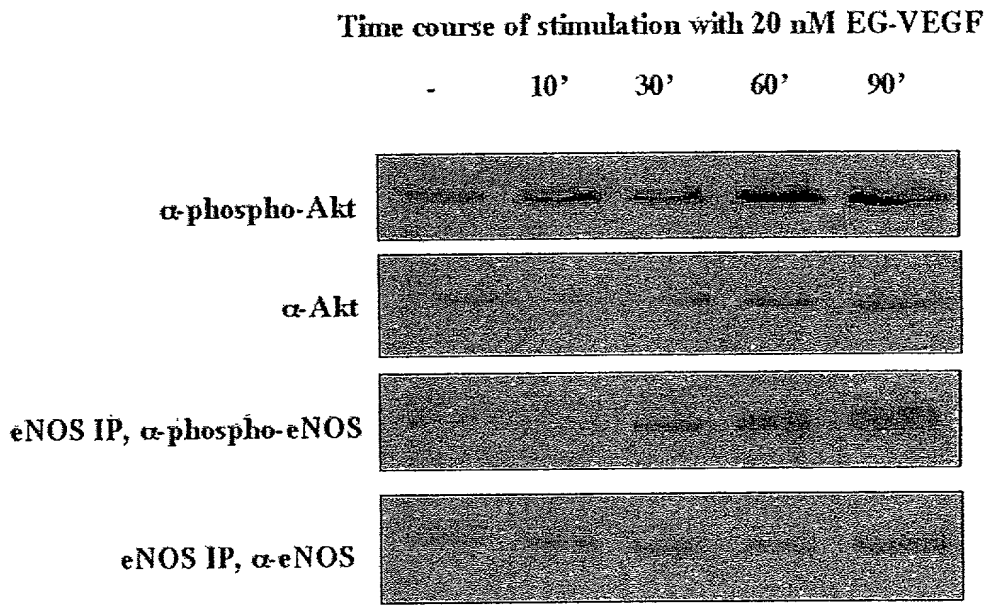

Time course of stimulation with 20 nM EG-VEGF
-
10'
30'
60'
90'
α-phospho-Akt
α-Akt
eNOS IP, α-phospho-eNOS
eNOS IP, α-eNOS

FIGURE 28

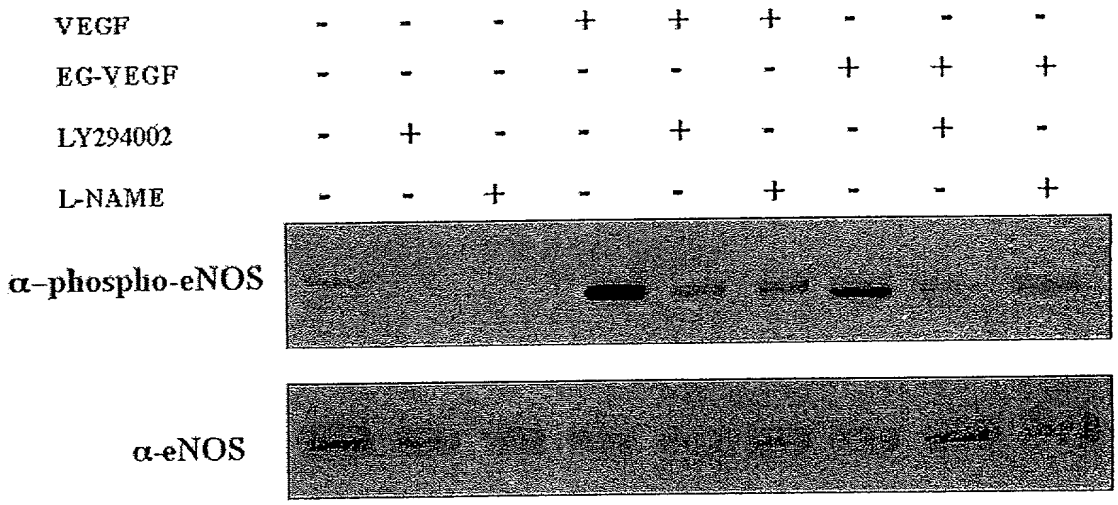
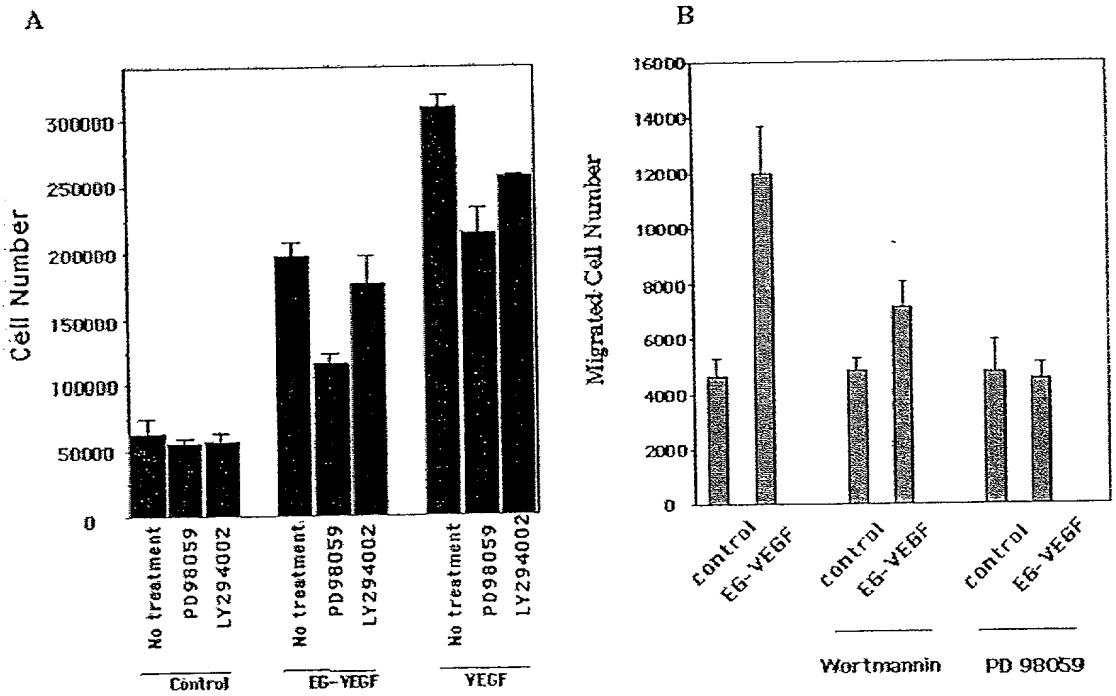


FIGURE 29


A
Cell Number
300000
250000
200000
150000
100000
50000
0
No treatment
PD98059
LY294002
No treatment
PD98059
LY294002
No treatment
PD98059
LY294002
Control
EG-VEGF
VEGF
B
Migrated Cell Number
16000
14000
12000
10000
8000
6000
4000
2000
0
control
EG-VEGF
control
EG-VEGF
control
EG-VEGF
Wortmannin
PD 98059